의학석사학위논문

Significance of Total Liver Volume on Hepatic Symptoms and Complications in ADPKD

상염색체우성다낭신에서 간의 부피가 간 관련 증상 및 합병증에 미치는 영향

2014 년 7 월

서울대학교대학원

임상의과학과 석사과정

김현숙

A thesis of the Degree of Master

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July 2014

Department of Clinical Medical Sciences

Seoul National University

College of Medicine

Hyunsuk Kim

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지도 교수 안 규 리

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김 현 숙

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2014년 07월

위 원 장 _____ (인)

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Significance of Total Liver Volume on Hepatic Symptoms and Complications in ADPKD

by

Hyunsuk Kim

A thesis submitted in partial fulfillment of the requirements for the Degree of

Master in Internal Medicine at Seoul National University College of Medicine

July 2014

Approved by Thesis Committee:

Professor _____Chairman

Professor _____Vice chairman

Professor _____

ABSTRACT

Introduction

Hepatic cysts are the most frequent extra-renal manifestation of autosomal dominant polycystic kidney disease (ADPKD). I investigated relationship of both hepatic symptoms and complications with the height-adjusted total liver volume (htTLV) in a cross-sectional study involving 461 subjects with Korean ADPKD patients.

Methods

Hepatic cysts involvement was defined as the presence of at least four liver cysts on a CT scan. Medical records were reviewed, and physical examinations were undertaken to identify hepatic symptoms and complications. A questionnaire was also used to evaluate hepatic cyst-related symptoms in a subset of patients. TLV was measured by stereotactic method and then adjusted by the height of the subject.

Results

Hepatic cysts involvement was more common among women in all age (96.2% vs. 86.9%, $P < 0.001$). The most common symptom in all subjects was back pain (59.4%), followed by flank pain (53.1%), abdominal fullness (46.5%), and dyspnea or chest discomfort (44.3%). Presence of pressure-related symptoms including early satiety, dyspnea or chest discomfort, sense of a mass and abdominal fullness, as well as pain and gastrointestinal symptoms were associated with htTLV ≥1,600 mL/m ($P < 0.001$). Additionally, the case of pressure-related complications,-including hepatic cyst infection or cholangitis were also related to htTLV ≥1,600 mL/m ($P < 0.001$). The

common complications in all subjects were ascites (16.6%), bilateral leg edema (5%), hernia (3.6%) and cyst infection (3.1%). Presence of pressure-related complications, including ascites, hernia, bilateral leg edema, biliary dilatation, and IVC stenosis or thrombosis, were associated with htTLV ≥ 2,100 mL/m. However, hepatic cyst infection or cholangitis were not related to htTLV ≥ 2,100 mL/m in multivariate models.

Conclusion

Clinicians should pay more attention to symptoms in cases with htTLV ≥1,600 mL/m and complication in ADPKD subjects with htTLV ≥2,100 mL/m.

Keywords: autosomal dominant polycystic kidney disease, hepatomegaly, symptoms, complications, liver volume

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LIST OF ABBREVIATIONS

ADPKD	autosomal dominant polycystic kidney disease
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate aminotransferase
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease epidemiology
CT	computed tomography
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ESRD	end stage renal disease
GI	gastrointestinal
hsCRP	high sensitivity C-reactive protein
htTKV	height-adjusted total kidney volume
htTLV	height-adjusted total liver volume
IDMS	isotope dilution mass spectrometry
IHD	intrahepatic duct
IQR	interquartile range
IVC	inferior vena cava
K/DOQI	National Kidney Foundation-Kidney Disease Outcomes Quality Initiative
LT	liver transplantation
Lt.	left
MRI	magnetic resonance imaging
Rt.	right

RUQ	right upper quadrant
TC	total cholesterol

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent potentially lethal monogenic disorder. It is characterized by the development of renal cysts and various extra-renal manifestations (1, 2). Although the most common extra-renal manifestation is hepatic cysts (3), morbidity in ADPKD patients is primarily determined by the severity of the underlying renal cystic disease and loss of renal function. Furthermore, most patients with hepatic cysts are thought to be asymptomatic (4). Therefore, physicians generally do not consider hepatic cysts as significant as polycystic kidney disease in ADPKD patients.

The prevalence of hepatic cyst involvement ranges from 70% to 94% detected by MRI studies (2, 3). The risk factors for severe hepatic cysts include advanced age, female sex, pregnancy, exogenous use of female steroid hormones, the degree of renal cystic disease, and the severity of renal dysfunction (5). The reported symptoms and signs of hepatic cysts include abdominal pain, dyspnea, early satiety, gastro-esophageal reflux, nausea, vomiting, and mechanical lower back pain (4, 6). The complications of hepatic cysts include ascites, cyst hemorrhage, cyst infection, and compression of adjacent structures such as hepatic veins (Budd-Chiari syndrome), IVC, portal veins or bile ducts. These symptoms and complications may be related to a progressive increase in the size and number of liver cysts. Therefore, disease management has been focused on decreasing the liver volume (6, 7).

However, determining which patients are affected, the optimal treatment timing, and effective interventions for hepatic cysts are unresolved issues. Although some treatment guidelines for hepatic cysts have been proposed (8), specific data required to resolve the aforementioned issues are limited. Furthermore, the associations of total liver volume with the symptoms and complications of hepatic cysts are poorly understood. Moreover, there is no standard definition of severe liver disease.

Therefore, this study aimed to elucidate the significance of height-adjusted total liver volume (htTLV) in pressure-related symptoms and complications in ADPKD. In particular, htTLV was measured by using a 3-D reconstruction method. The distribution of htTLV, as well as inter- and intra-familial variations in Korean ADPKD patients were also investigated. In addition, the associations of htTLV with hepatic symptoms and complications were elucidated.

SUBJECTS AND METHODS

1. Patients

This study was approved by the Seoul National University Hospital Review Board (H-1002-028-309). All the patients gave their written informed consent to participate in this study, and this study was undertaken in accordance with the Declaration of Helsinki.

I conducted a cross-sectional study of 488 subjects who were registered and had undergone regular follow-ups, including biennial abdominal computed tomography (CT) scans, within 2 years from registration, at the ADPKD clinic of Seoul National University Hospital between October 2009 and September 2012. The ages of the subjects were confined to above 20 years. ADPKD was diagnosed with the unified criteria (9). All the subjects underwent evaluations that included their detailed medical history, hepatic and renal functions, and CT scans that were taken using a multi-detector CT scanner (Somatom Sensation 16, SIEMENS; Light speed Ultra 8, GE; Brilliance CT 64, Philips; and Somatom Definition, SIEMENS). A total of 488 subjects were retrospectively screened for eligibility, and 461 patients were selected (Figure 1). Patients who had any type of cancer with active treatment (n = 2) or had either a change in their liver size or any possibility of such a change occurring (n = 25), such as in subjects with cancer with liver metastasis (n = 1), hepatocellular carcinoma with hepatectomy (n = 1), liver cirrhosis (n = 4), chronic HBV hepatitis (n = 16), chronic HCV hepatitis (n = 2), and hepatectomy due to intrahepatic duct stones (n = 1) were excluded. Hepatic cysts involvement was defined as a condition with at least four liver cysts in the CT scan (6, 10). Among 461 subjects, 423 (91.8%) had liver cysts and 38 had no liver cyst or had less than four. A symptom questionnaire was obtained from a subset of 253 subjects. In addition, 13 patients had undergone interventions related to large hepatic cysts. Four patients had undergone liver transplantation (LT); four, hepatectomy; and five, hepatic embolization. These patients were included in the complications analysis but excluded from the symptoms analysis. Therefore, we conducted complication analysis for 461 patients and symptom analysis for 253 patients.

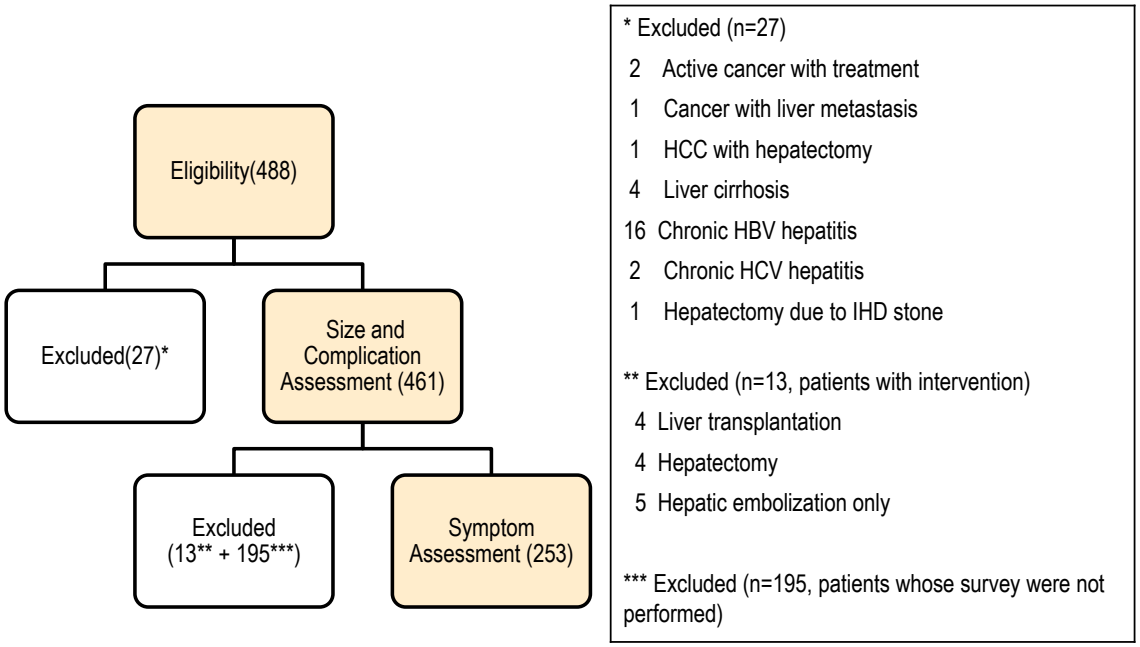


Figure 1. Study flow chart

2. Clinical assessment

Chronic hepatic symptoms were retrospectively evaluated by using a questionnaire, and complications were identified through a review of medical records. The following data were collected: the baseline demographic profiles (age, sex, height and weight), medical history [hypertension, cancer, chronic liver disease, chronic kidney disease (CKD) stage, prevalence of end-stage renal disease (ESRD), and onset age of ESRD], and laboratory results [serum albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol (TC), high-sensitivity C-reactive protein (hsCRP) and creatinine].

Hypertension was defined as systolic/diastolic blood pressure >140/90 mmHg or a history of antihypertensive medication according to medical records. Chronic liver disease was defined as chronic hepatitis (toxic, alcoholic, viral, or autoimmune) or liver cirrhosis. CKD stages were classified according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines (11). ESRD was defined as an estimated glomerular filtration rate (eGFR) <15 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ or the initiation of renal replacement therapy.

Serum creatinine was measured using the Jaffe method with Hitachi 7600 or Toshiba-200FR, and as traceable to the IDMS. The Chronic Kidney Disease EPIdemiology (CKD-EPI) collaboration formula was used to calculate the eGFR.

3. Measurement of liver and kidney volumes

Total liver volume (TLV) was measured by stereotactic volumetry, in which the total volume was calculated from a set of contiguous images by summing the products of the area measurements and slice thickness. Rapidia 2.8 CT software (INFINITT, Seoul, Korea) was used as the volumetric tool. Rapidia is semi-manual software for volumetry and 3-D reconstruction. It has been adopted in a previous study to measure liver size in ADPKD and is used in many studies to calculate 3-D volume of organs (12). Large vascular structures such as the IVC or portal veins were outlined manually and excluded from the TLV. Meanwhile, total kidney volume (TKV) was calculated by the modified ellipsoid method (13). Although volumetry

would be the most accurate, using the stereotactic method (by Rapidia version 2.8) was very time consuming (1 hour/case); the pilot study showed that TKV calculated by the modified ellipsoid method and stereotactic method using Rapidia were strongly correlated (R^2 = 0.959). Therefore, the modified ellipsoid method was used to measure TKV. Both TLV and TKV (in mL) were adjusted by height (m); thus, height-adjusted TLV (htTLV) and TKV (htTKV) were used as variables for analysis.

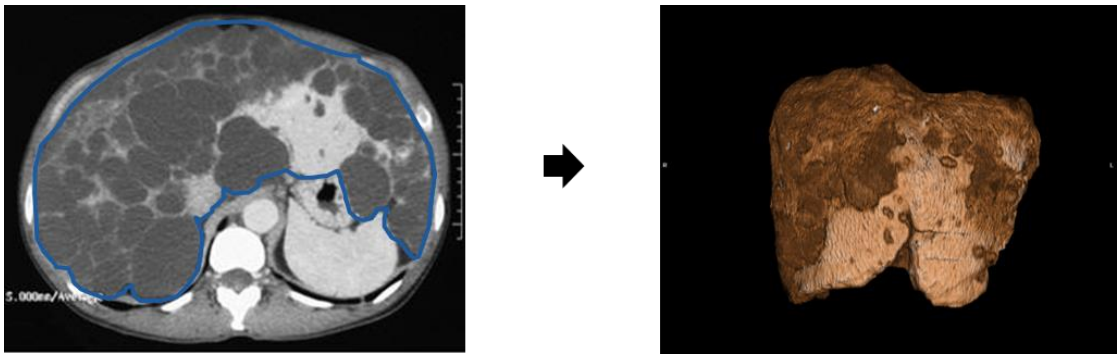


Figure 2. Stereotactic method for measuring TLV

4. Investigation of hepatic symptoms and complications

The hepatic symptoms were assessed with a questionnaire modified from Gastrointestinal Symptom Rating Scale (GSRS) (Table 1) (14). The questionnaire was generated to evaluate the hepatic symptom prevalence in ADPKD. The patient version is shown in Supplementary Table 1. The questionnaire had 11 questions in Korean, including questions concerning gastrointestinal (GI) and non-GI symptoms. Each question measured the severity or frequency of the symptoms, except for the question about the sense of a mass. All items, except for mass sensation, were graded from 0–3 points. The participants completed the questionnaire in the presence of an interviewer. The subjects of the questions were early satiety, palpable mass, decreased appetite, abdominal pain or discomfort, flank pain or discomfort, back pain or discomfort, dyspnea or chest discomfort, analgesics intake, nausea and vomiting, epigastric soreness, and abdominal fullness. The questions were grouped according to symptoms related to pressure (early satiety, dyspnea or chest discomfort, palpable mass, and abdominal fullness), pain [right upper quadrant (RUQ) pain or discomfort, flank pain or discomfort, back pain or discomfort, and analgesics intake), and the GI tract (nausea or vomiting, anorexia, and epigastric soreness). In addition, the interviewer physically examined the patients for the absence/presence of inguinal or umbilical hernia and grade of leg-pitting edema (grade 1: ≤2 mm and disappears in 3 seconds; grade 2: 2–4 mm and disappears in 10–15 seconds; grade 3: 4–6 mm and lasting >1 minute; and grade 4: 6–8 mm with the dependent extremity looking fuller and lasting as long as 2–5 minutes).

Table 1. Symptom questionnaire

Category	Hepatic symptoms	Grade of symptoms	score
Pressure-related	**Early satiety**	0 – No or transient events 1 – Occasional events interfering with some social activities 2 – Prolonged and troublesome events causing requests for relief and interfering with many social activities 3 – Severe or continuous events with impact on all social activities	**3**
	Sense of a mass	0 – Not palpable 1 – Palpable	**1**
	Dyspnea or chest discomfort	0 – No or transient events 1 – Occasional events interfering with some social activities 2 – Prolonged and troublesome events causing requests for relief and interfering with many social activities 3 – Severe or continuous events with impact on all social activities	**3**
	Abdominal distention	0 – No or transient events 1 – Occasional events interfering with some social activities 2 – Prolonged and troublesome events causing requests for relief and interfering with many social activities 3 – Severe or continuous events with impact on all social activities	**3**
Pain	**RUQ pain or discomfort**	0 – No or transient events 1 – Occasional events interfering with some social activities 2 – Prolonged and troublesome events causing requests for relief and interfering with many social activities 3 – Severe or continuous events with impact on all social activities	**3**
	Flank pain or discomfort	0 – No or transient events 1 – Occasional events interfering with some social activities 2 – Prolonged and troublesome events causing requests for relief and interfering with many social activities 3 – Severe or continuous events with impact on all social activities	**3**

Category	Hepatic symptoms	Grade of symptoms	score
	Back pain or discomfort	0 – No or transient events 1 – Occasional events interfering with some social activities 2 – Prolonged and troublesome events causing requests for relief and interfering with many social activities 3 – Severe or continuous events with impact on all social activities	**3**
	Taking analgesics	0 – None or transient 1 – Occasional 2 – Once in a week 3 – Almost every day	**3**
GI	**Anorexia**	0 – No or transient events 1 – Occasional events interfering with some social activities 2 – Prolonged and troublesome events causing requests for relief and interfering with many social activities 3 – Severe or continuous events with impact on all social activities	**3**
	Nausea or vomiting	0 – None 1 – Occasional events interfering with some social activities 2– Frequent nausea, no vomiting 3 – Nausea almost every day and frequent vomiting	**3**
	Epigastric soreness	0 – No or transient events 1 – Occasional events interfering with some social activities 2 – Prolonged and troublesome events causing requests for relief and interfering with many social activities 3 – Severe or continuous events with impact on all social activities	**3**
			Total 31

Medical records and CT findings were reviewed for the following hepatic complications: ascites, cyst infection, cyst rupture, inguinal or umbilical hernia, cholangitis, biliary dilatation, IVC stenosis, bilateral leg edema, Caroli disease, and splenomegaly without chronic liver disease. Complications were reviewed from medical records; CT interpretations were additionally reviewed in cases of ascites, cyst rupture, or biliary dilatation. Ascites were classified into 3 categories as follows: small, minimal layer of ascites in the gravity-dependent regions of the peritoneal and/or perihepatic cavity; moderate, presence of fluid in the paracolic gutters; and large, sufficient ascites to displace the small intestinal loops. Complications were defined as events occured from Oct 2008 until the investigation was compleleted.

Cyst infection was defined as aspiration of an infected cyst; positive findings on CT, MRI, or renal ultrasonography; or definite tenderness at a cystic lesion and signs of infection. Cyst rupture was defined as disrupted cyst wall on CT and compatible history such as pain or hemorrhage. Biliary dilatation was defined as abnormal extrahepatic or intrahepatic dilatation due to hepatic cyst compression. Cholangitis was defined as the presence of fever, abdominal pain, direct bilirubinemia, and/or positive blood culture. Splenomegaly was defined as the largest dimension of the spleen exceeding 11 cm. Hernia and bilateral leg edema were confirmed by physical examination. IVC stenosis was defined as stenosis or obliteration due to pressure or thrombosis and IVC stent insertion.

On the basis of the assumption that compressed large blood vessels (e.g., the IVC) cause vascular insufficiency and consequent leg edema, bilateral leg edema was included as a complication. Complications were classified as pressure-related complications (ascites, hernia, bilateral leg edema, biliary dilatation, and IVC stenosis), infections (cyst infections and cholangitis), or others (splenomegaly and Caroli disease). Hemorrhagic cysts were excluded from the list of complications because they were hardly differentiated by CT scans (e.g., high protein contents) and their clinical significance was unclear.

5. Inter- and intra-familial variations in ADPKD

An additional analysis of 54 families (n = 123) of the study population was performed. The htTLV of each family was plotted, and the pattern of familial distribution was investigated. The proband of each family was defined as the individual with the largest liver. The htTLV of each family member above 40 years old was plotted with the set of probands along the x-axis, and the mean htTLV was compared according to a cut-off of 1,600 mL/m.

6. Statistical analysis

The prevalence of liver cysts and the distribution of the htTLV were analyzed using Chi-square test, Fisher's exact test, and the Mann-Whitney test. Log odds graphs of the complications or symptoms according to the htTLV were plotted using R Statistical software (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/). The clinical characteristics based on the htTLV were analyzed using an ANCOVA test for age and sex adjustment. The prevalence of the symptoms and complications was described with an ANCOVA test adjusted for age and sex. Multivariate binominal logistic regression analysis of the complications was performed and adjusted for variables that showed significant associations ($P < 0.05$) in the univariate analysis. The data were statistically analyzed with SPSS version 19.0 software (SPSS, Chicago, IL, USA). All the reported P values were two-tailed, and the statistical significance threshold was set at $P < 0.05$.

RESULTS

PART I

Distribution of htTLV in ADPKD

1. Baseline characteristics according to sex

The mean age of all the subjects was 51, and 52% of them were female (n = 241). The medians (IQR) of the htTLV and the htTKV were 986 (825 and 1280) and 820 (453 and 1345), respectively. No significant gender differences were noted for age and medians of htTLV and htTKV. In terms of kidney-related variables, the prevalence of hypertension was 79% (n = 365) and was significantly higher in male subjects ($P < 0.001$).The eGFR was not different between male and female subjects. Because all the subjects had undergone CT scans, there were few subjects with stage 4 CKD were excluded (n = 24, 5.2% of all the subjects) due to selection bias (Table 2).

Table 2. Baseline characteristics according to sex

Variable		Total	Male	Female	P value [a]
n (%)		461(100)	220(48)	241(52)	
htTLV [median, IQR]		986(825, 1280)	1024(825, 1481)	981(825, 1149)	0.066
Age [mean ± SD]		51.3 ± 12.6	50.1 ± 13.8	52.5 ± 11.3	0.069
Age group [n(%)]	-39	81(17.6)	50(22.6)	31(12.9)	0.005
	40-49	121(26.2)	57(25.8)	64(26.7)	
	50-59	139(30.2)	57(25.8)	82(34.2)	
	60-69	79(17.1)	37(16.7)	42(17.5)	
	70-	41(8.9)	20(9.0)	21(8.8)	
Hypertension [n(%)]		365(79.2)	193(87.3)	172(71.7)	<0.001
eGFR*(CKD-EPI)		80.0 ± 27.7	74.2 ± 27.6	69.8 ± 27.7	0.131
CKD stage	Stage 1	101(22.7)	47(21.8)	54(23.6)	0.094
	Stage 2	132(29.7)	65(30.1)	67(29.3)	
	Stage 3	94(21.1)	49(22.7)	45(19.7)	
	Stage 4	24(5.4)	17(7.9)	7(3.1)	
	Stage 5	94(21.1)	38(17.6)	56(24.5)	
htTKV [median, IQR]		820(453, 1345)	881(484, 1356)	768(425, 1322)	0.113

[a] P value of sex difference by Man-Whitney test and Fisher's Exact test, *excluded renal replacement therapy or kidney transplantation (94 cases), Abbreviations: htTLV, height-adjusted total liver volume; eGFR (CKD-EPI), estimated glomerular filtration rate (Chronic kidney disease epidemiology); htTKV, height-adjusted total kidney volume

2. Prevalence of hepatic cysts involvement according to age and sex

As shown in Figure 3 and Table 3, the prevalence of liver cysts was 91.8% (n = 423) of the all subjects. In detail, 96.2% of the female subjects and 86.9% of the male subjects had hepatic cysts involvement ($P < 0.001$). Among age groups, female predominance was significant in the youngest group (< 39 years) (96.8% of the female vs. 74.0% of the male subjects, $P < 0.001$).

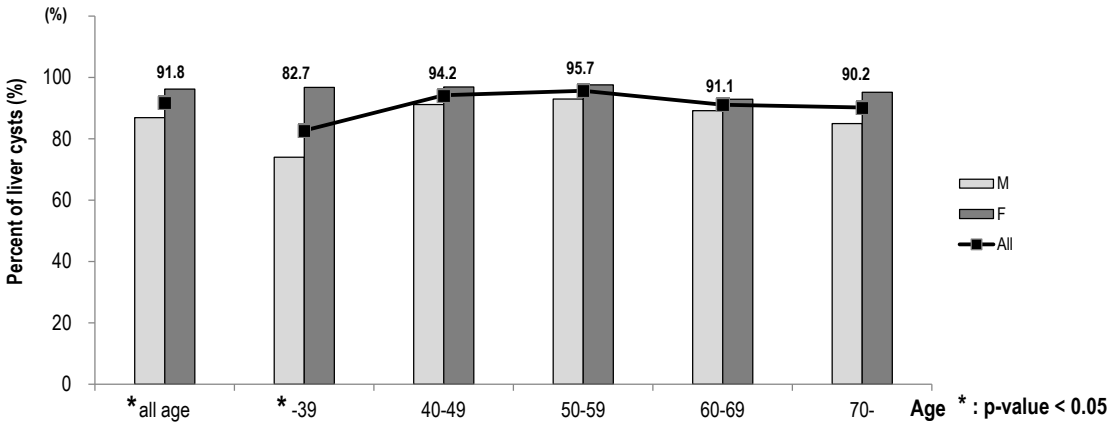


Figure 3. Prevalence of hepatic cysts involvement according to age and sex

Table 3. Prevalence of hepatic cysts involvement according to age and sex

Sex	Age					
	All age	-39	40-49	50-59	60-69	70-
Total	461	81	121	139	79	41
All [n(%)], n=461	423(91.8)	67(82.7)	114(94.2)	133(95.7)	72(91.1)	37(90.2)
Male [n(%)], n=221	192(86.9)	37(74.0)	52(91.2)	53(93.0)	33(89.2)	17(85.0)
Female [n(%)], n=240	231(96.2)	30(96.8)	62(96.9)	80(97.6)	39(92.9)	20(95.2)
Male vs. Female, P value[a]	<0.001	<0.001	0.252	0.227	0.700	0.343

[a] χ^2 test or Fisher's exact test as appropriate

3. Proportion of hepatomegaly according to htTLV

Figure 4 and Table 4 show the distribution of htTLV and hepatomegaly by sex. The mean ± SD htTLV of both sexes was 1,298 ± 1,055 mL/m; the mean htTLV of men was 400 mL/m less than that of women ($P < 0.05$); however, the median did not differ significantly between sexes. The overall distribution of the study population was skewed left. When the total subjects were divided into tertiles and quartiles, the mean htTLV of the 3rd tertile and 4th quartile were significantly higher in female patients (male vs. female, 3rd tertile: 55(25%) vs. 99(41%); 4th quartile: 37(17%) vs. 78(32%), $P < 0.001$). Accordingly, the proportion of hepatomegaly was greater among female patients than male patients. When htTLV was natural log-transformed, the distribution of ln(htTLV) and proportion of hepatomegaly were similar (Figure 5 and Table 5).

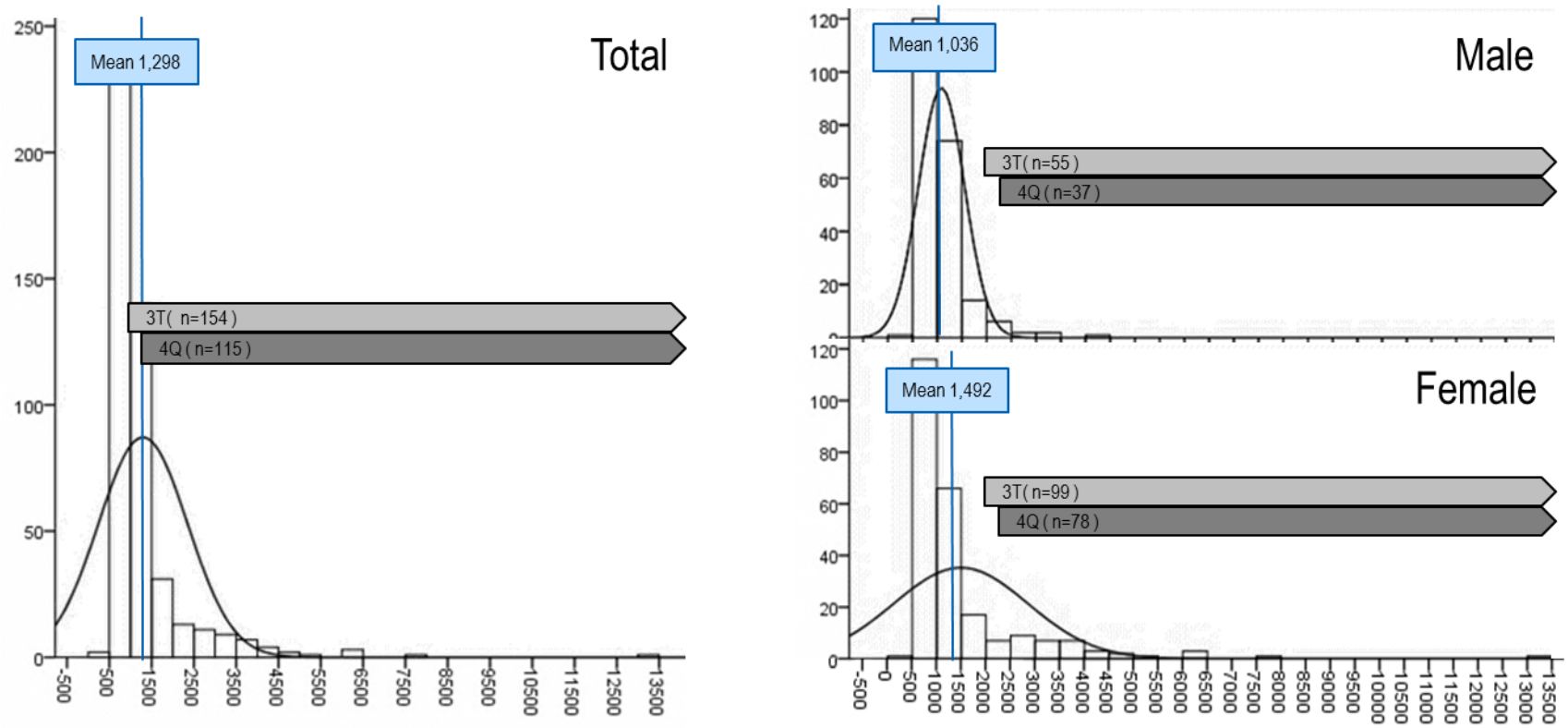


Figure 4. Proportion of hepatomegaly according to htTLV, 3T: highest tertile of both sexes, 4Q: highest quartile of both sexes.

Table 4. Proportion of hepatomegaly according to htTLV

n(%) of each tertile (total subjects)	Total (n=461)	M (n=221)	F (n=240)	P value of sex difference [a]
1st tertile (460-886)	153(33)	70(32)	83(34)	
2nd tertile (887-1,137)	154(33)	95(43)	59(25)	
3rd tertile (1,139-13,412)	154(33)	55(25)	99(41)	<0.001
1st quartile (460-824)	115(25)	55(25)	60(25)	
2nd quartile (827-986)	115(25)	60(27)	55(23)	
3rd quartile (989-1,283)	116(25)	68(31)	48(20)	
4th quartile (1,299-)	115(25)	37(17)	78(32)	<0.001

[a] Fisher's exact test, Abbreviation: htTLV, height-adjusted total liver volume

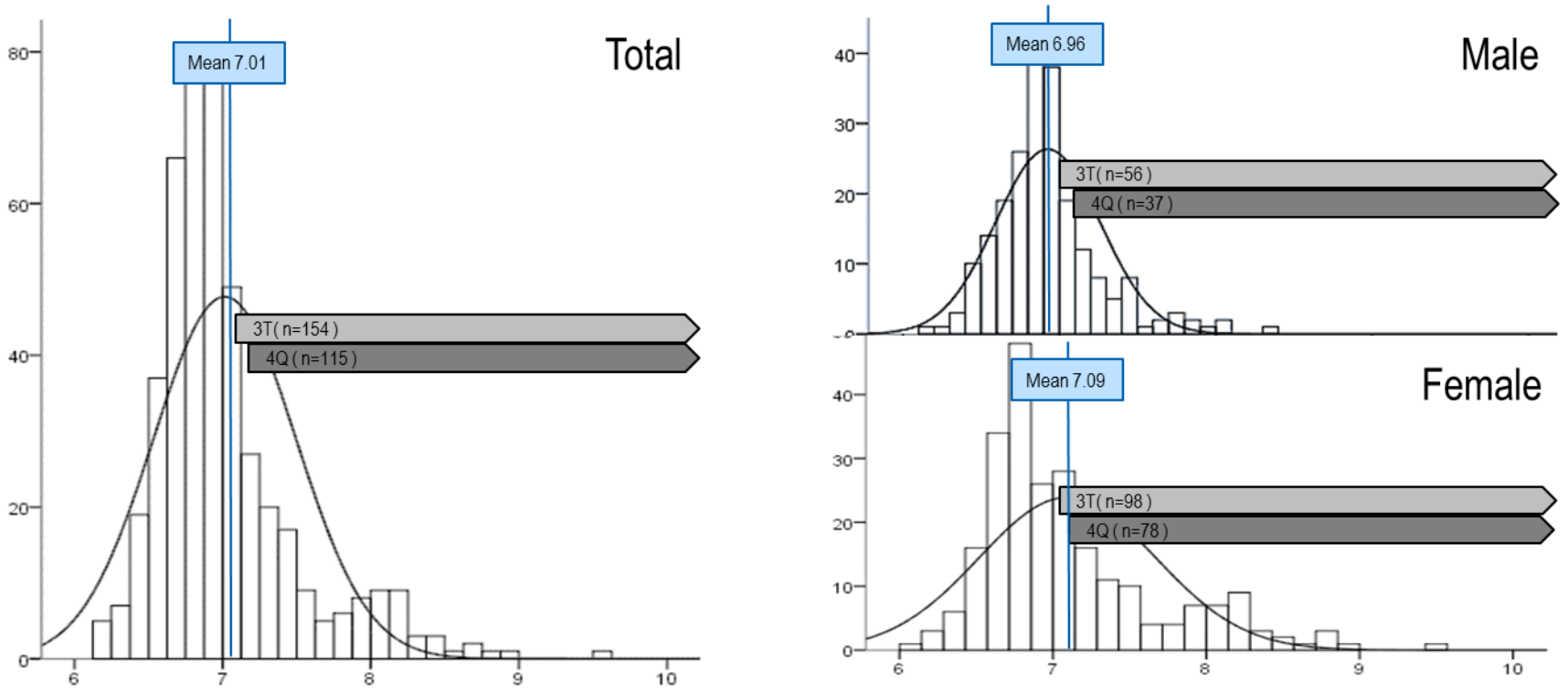


Figure 5. Proportion of hepatomegaly according to Ln(htTLV), 3T: highest tertile of both sexes, 4Q: highest quartile of both sexes.

Table 5. Proportion of hepatomegaly according to ln(htTLV)

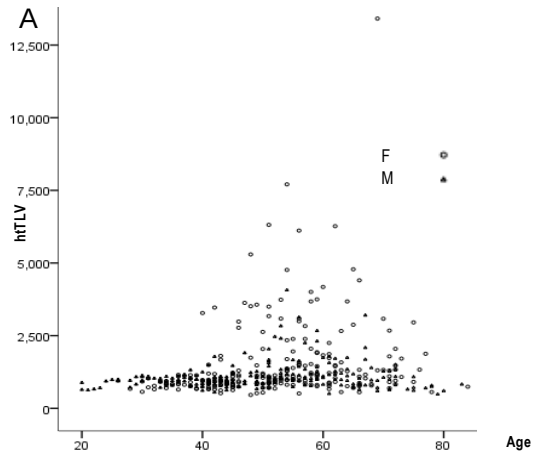
n(%) of each tertile (total subjects)	Total (n=461)	M (n=221)	F (n=240)	P value [a]
1st tertile (6.13-6.79)	153(33)	70(32)	83(34)	
2nd tertile (6.79-7.04)	154(33)	95(43)	59(25)	
3rd tertile (7.04-9.50)	154(33)	55(26)	99(41)	<0.001
1st quartile (6.13-6.71)	115(25)	55(25)	60(25)	
2nd quartile (6.72-6.89)	115(25)	60(27)	55(23)	
3rd quartile (6.90-7.16)	116(25)	68(31)	48(20)	
4th quartile (7.16-9.50)	115(25)	37(17)	78(32)	<0.001

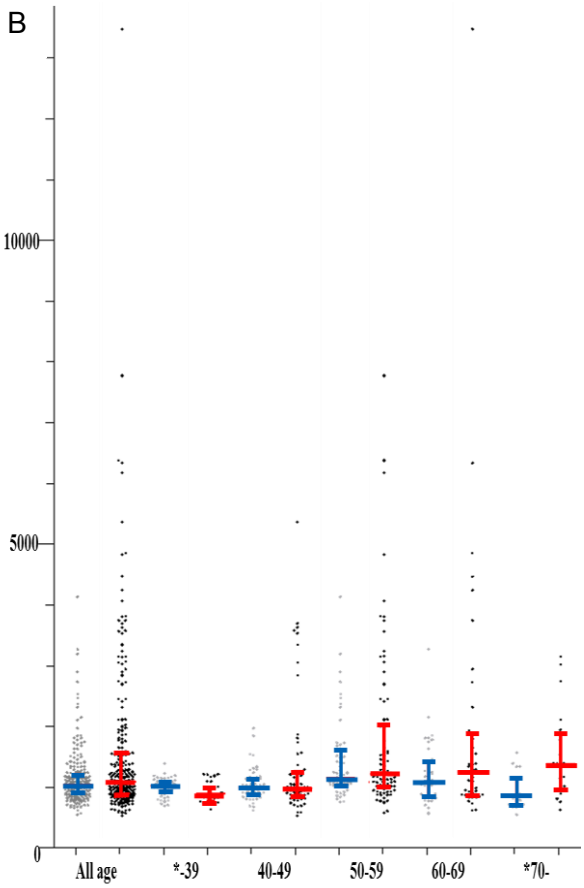
[a] Fisher's exact test, Abbreviation: htTLV, height-adjusted total liver volume

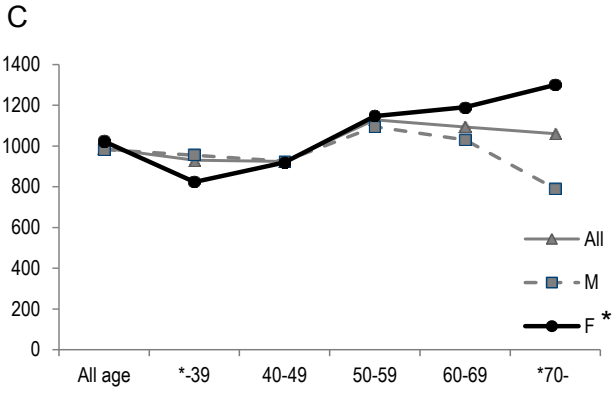
4. Distribution of htTLV according to age groups and sex

The distributions of htTLV with respect to age and sex are shown in Figure 6 and Table 6. The distribution of htTLV with respect to sex showed female patients had extreme hepatomegaly (Figure 6-A). However, with respect to sex and age, the overall median htTLV did not differ significantly between sexes (Figure 6-B, Table 6). Median (IQR) htTLV was significantly greater in males aged <39 years (955 [867, 1,029] mL/m) than females of the same age (823 [722, 942] mL/m, $P = 0.017$). Among patients aged >50 years, median htTLV was greater in females, although the difference was not significant. Meanwhile, among patients aged >70 years, median htTLV was significantly higher among females (1300 [890, 1,750] mL/m) than males (791 [650, 1,086] mL/m, $P = 0.005$). Among males aged >60 years, htTLV decreased slightly with increasing age; however, median htTLV in females increased consistently with age ($P < 0.001$, Jonckheere–Terpstra test, P for trend of non-parametric tests).

In patients with non-hepatic cysts ($n = 38$), the median htTLV was 831 (702, 979) mL/m, ranging from 484 to 979 mL/m.


A
12,500
10,000
7,500
5,000
2,500
0
hTLV
F
M
20
40
60
80
Age


B
10000
5000
0
All age
*-39
40-49
50-59
60-69
*70-


C
1400
1200
1000
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All age
*-39
40-49
50-59
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All
M
F *

Figure 6. Distribution of htTLV according to age groups and sex. (A) Scatter plot of htTLV; (B) Scatter plot of htTLV by age groups and sex, * P < 0.05; (C) Trend in median of htTLV according to age groups and sex, * P value for Jonckheere-Terpstra test (P for trend of non-parametric tests) <0.001

Table 6. Distribution of htTLV according to age groups and sex

Sex	htTLV	Age group					
		All age	*-39	40-49	50-59	60-69	*70-
All	median(IQR)	989 (825, 1291)	930 (772,1028)	924 (817, 1105)	1,128 (948,1664)	1,093 (812, 1581)	1,060 (730,1332)
M	median(IQR)	982 (825,1156)	955 (867,1029)	925 (826,1071)	1,095 (968,1590)	1,030 (796,1369)	791 (650,1086)
F	median(IQR)	1,023 (824,1477)	823 (722,942)	919 (803,1192)	1,147 (940,1939)	1,190 (816,1840)	1,300 (890,1750)
Male vs. Female, P value[a]		0.066	0.017	0.755	0.625	0.216	0.005

[a] Mann-Whitney test, * P < 0.05, Abbreviation: htTLV, height-adjusted total liver volume

5. Correlation between htTLV and htTKV or (htTKV+htTLV)

There was a weak correlation between htTKV and htTLV (R^2 = 0.062, Figure 7-A). However, htTLV was strongly correlated with htTKV+htTLV (R^2 = 0.626, Figure 7-B). This suggests hepatic symptoms are more closely related to the volume of intra-abdominal mass (i.e., htTKV+htTLV) in ADPKD. Furthermore, htTKV+htTLV had more higher OR with the likelihood of symptom presentation than htTLV only (Figure 7-C and D). However, because the present study focused on htTLV, symptoms, and complications, htTLV was adopted as a representative indicator of intra-abdominal mass, and the relationships between htTLV and hepatic symptoms were analyzed.

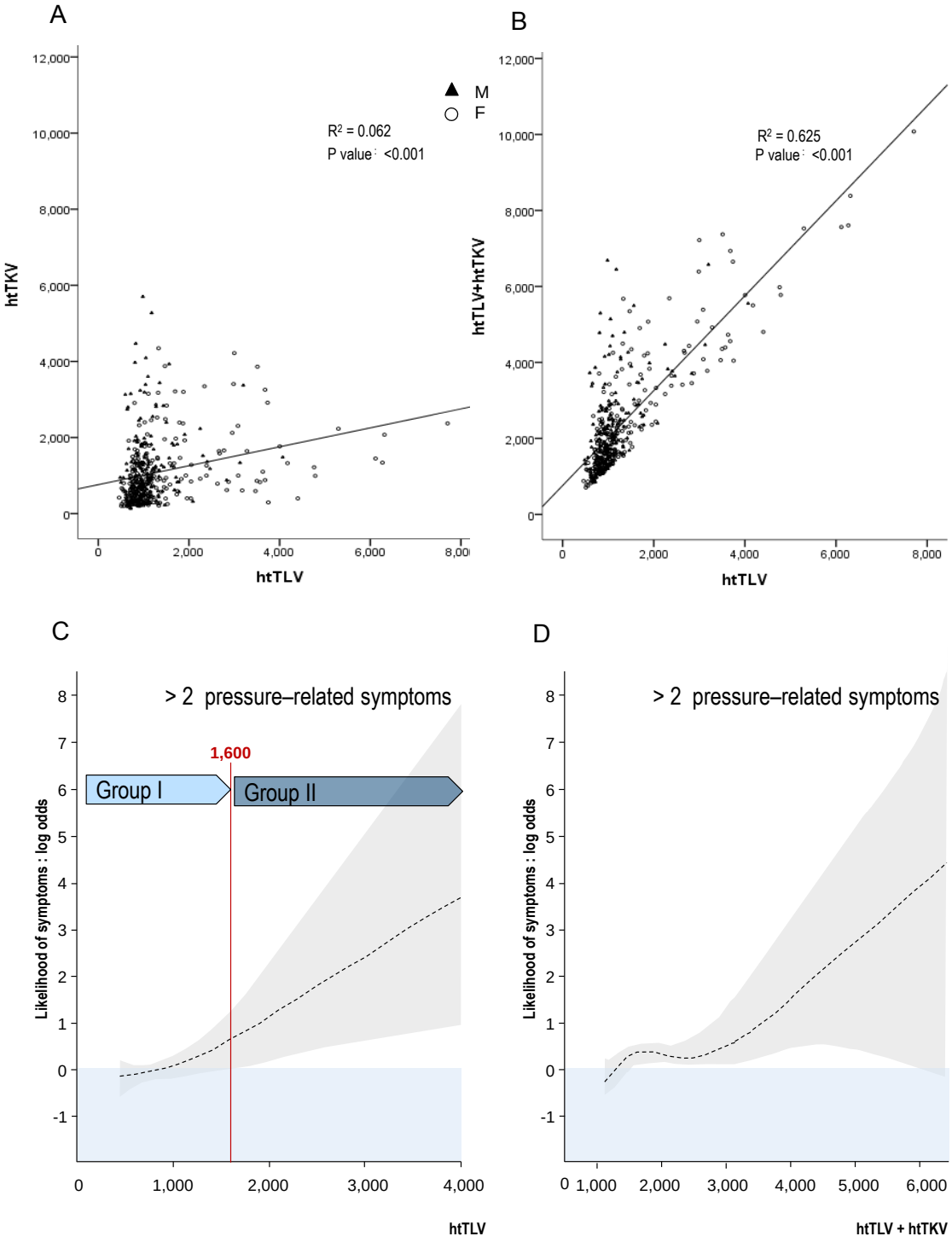


Figure 7: Correlation between htTLV and htTKV or (htTKV+htTLV). (A) Correlation between htTLV (B) Correlation between htTKV or (htTKV+htTLV) (C) Likelihood of having two or more pressure–related symptoms according to htTLV (D) Likelihood of having two or more pressure–related symptoms according to htTLV + htTKV

PART II

Relationships between htTLV and hepatic symptoms

1. Prevalence and likelihood of hepatic symptoms

The frequencies of symptoms are shown in Figure 8-A. The most common symptom was back pain (58.8%), followed by flank pain (53.1%), abdominal fullness (46.5%), and dyspnea or chest discomfort (44.3%). The most frequent symptom affecting quality of life was abdominal fullness (7.9%), followed by early satiety (5.3%) and RUQ pain (3.1%).

The likelihood of having at least 2 pressure-related symptoms (log odds) with respect to htTLV is shown in Figure 8-B. Pressure-related symptoms were analyzed in the present study, because they are thought to be more representative and correlated with htTLV-related symptoms. To increase the sensitivity of correlation analysis, the presence of more than 2 symptoms was used as cut-off. The log odds of having at least 2 pressure-related symptoms increased as htTLV increased (Figure 8-A). At approximately 1,600 mL/m, the probability of having constant symptoms increased with increasing htTLV ± 2SD. In addition, when htTLV was >1,600 mL/m, the log odds was always positive; in other words, when htTLV was ≥1,600 mL/m the odds of having ≥2 pressure-related symptoms will always be >1. Therefore, the patients were divided into 2 groups according to the cut-off of 1,600 mL/m: the htTLV <1,600 and ≥1,600 mL/m groups (Figure 8-B).

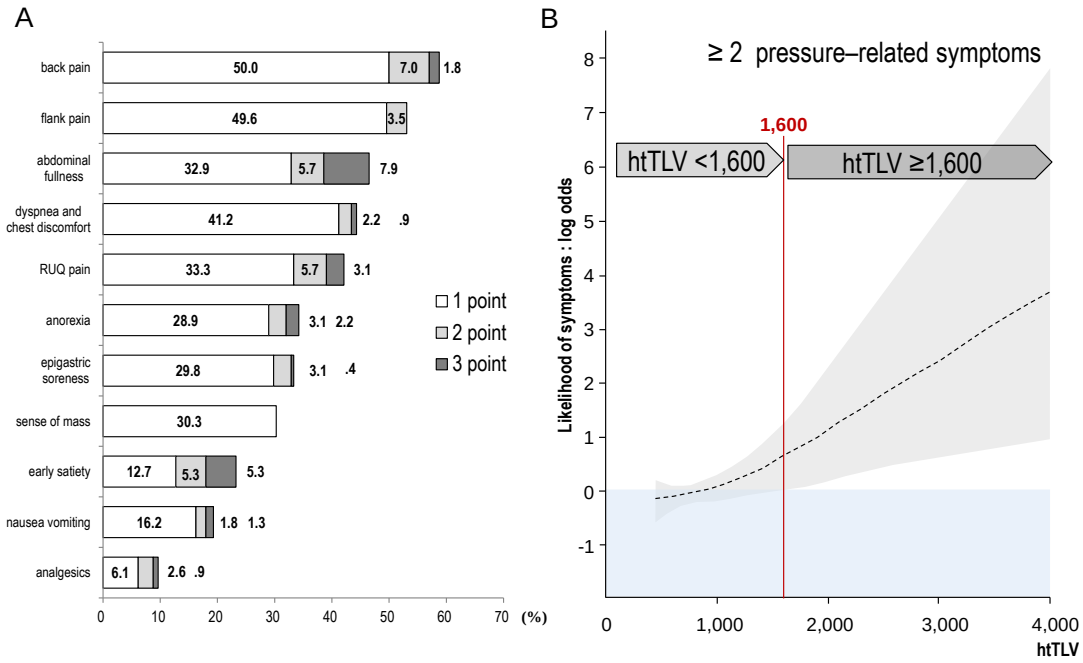


Figure 8. Prevalence and likelihood of hepatic symptoms. (A) Prevalence of hepatic symptoms (B) Likelihood of having two or more pressure–related symptoms

2. Distribution of htTLV according to a cut-off of 1,600 mL/m

The distribution of htTLV according to the cut-off in all patients, males and females separately and age group are shown in Figure 9. The percentage patients in the htTLV ≥1,600 mL/m group was greater among females than males (31% vs. 10%, P < 0.001) (Figure C and D). Female patients were more common in the htTLV ≥1,600 mL/m group in all age groups (Figure 9-D).

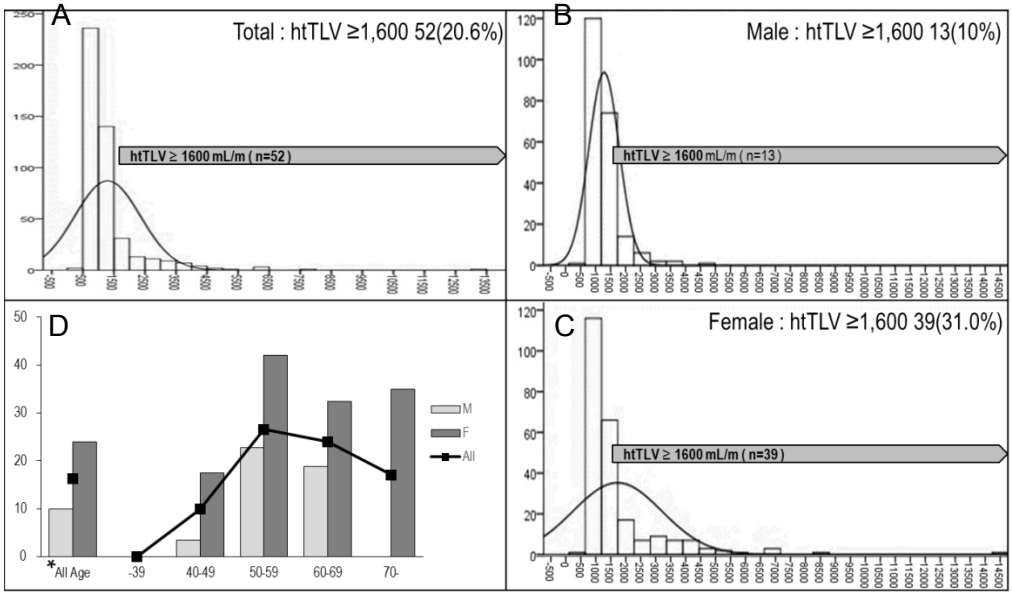


Figure 9. Distribution of the htTLV <1,600 and ≥1,600 mL/m groups by sex and age groups. (A) Distribution of total subjects (B) Distribution of male (C) Distribution of female (D) Distribution of htTLV ≥1,600 mL/m according to age and sex, * P < 0.001, χ^2 test.

3. Clinical characteristics of the htTLV <1,600 and ≥1,600 mL/m groups

The clinical characteristics of the htTLV <1,600 and ≥1,600 mL/m groups are shown in Table 7. A total of 253 patients filled out the symptom questionnaire. As htTLV was closely associated with age and sex, age- and sex-adjusted ANCOVA was used to analyze intergroup differences. The result shows that 20.6% and 79.4% of patients were in the htTLV <1,600 and ≥1,600 mL/m groups, respectively. The htTLV ≥1,600 mL/m group contained significantly more female patients. Patients in the htTLV <1,600 mL/m group were significantly younger. In the htTLV <1,600 and ≥1,600 mL/m groups, the median htTLV values were 934 and 2,646 mL/m, respectively; mean htTKV values were 723 and 1,338 mL/m, respectively ($P < 0.05$). There was no significant difference in the incidence of hypertension between groups. Mean eGFR was lower significantly lower in the htTLV ≥1,600 mL/m group. Regarding laboratory findings, albumin and total cholesterol levels were significantly lower the htTLV ≥1,600 mL/m group.

Table 7. Clinical characteristics of the high and low htTLV groups

All: 253		All	htTLV <1,600	htTLV t1,600	P value [a]
n(%)		253(100)	201(79.4)	52(20.6)	
Female [n(%)]		125(49.4)	86(42.8)	39(75.0)	<0.001
Age [mean ± SD]		50.1 ± 13.0	48.5 ± 13.7	55.8 ± 7.9	<0.001
htTLV [median(IQR)]		1013(849,1484)	934(808,1069)	2646(1979,3420)	<0.001
htTKV [median(IQR)]		855(464,1483)	723(436,1313)	1338(852, 2074)	<0.001
HTN [n(%)]		204(80.6)	157(78.1)	47(90.4)	0.182
eGFR*(CKD-EPI) [mean ± SD]		70.1 ± 27.9	73.1 ± 28.1	56.8 ± 21.7	<0.001
CKD stage	Stage 1	59(23.9)	56(28.3)	3(6.1)	<0.001
	Stage 2	71(28.7)	62(31.3)	9(18.4)	
	Stage 3	70(28.3)	51(25.8)	19(38.8)	
	Stage 4	12(4.9)	11(5.6)	1(2.0)	
	Stage 5	35(14.2)	18(9.1)	17(34.7)	
Albumin [mean ± SD]		4.3 ± 0.4	4.4 ± 0.3	4.0 ± 0.5	<0.001
TC [mean ± SD]		176.9 ± 28.5	179.5 ± 28.1	166.1 ± 28.0	<0.001

[a] ANCOVA adjusted for age and sex, *excluded RRT or KT (35 cases), Abbreviations: htTLV, height-adjusted total liver volume; eGFR (CKD-EPI), estimated glomerular filtration rate (Chronic kidney disease epidemiology); htTKV, height-adjusted total kidney volume; TC, total cholesterol

4. Prevalence and severity of symptoms in the htTLV <1,600 and ≥1,600 mL/m groups

Only a few items on the questionnaire were scored 2 or 3 points. Therefore, only the presence or absence of each symptom was analyzed (Figure 10). Overall, both groups exhibited a very high frequency of symptoms. There were significant differences between groups for in all symptoms except for flank pain. RUQ pain was very common in both groups. However, the ratios of analgesics intake in the htTLV <1,600 and ≥1,600 mL/m groups were 22.0% and 6.2%, respectively. The prevalences of RUQ pain (72.0%) and back pain (68.0%) were significantly higher in the htTLV ≥1,600 mL/m group, but there was no significant difference between groups with respect to flank pain.

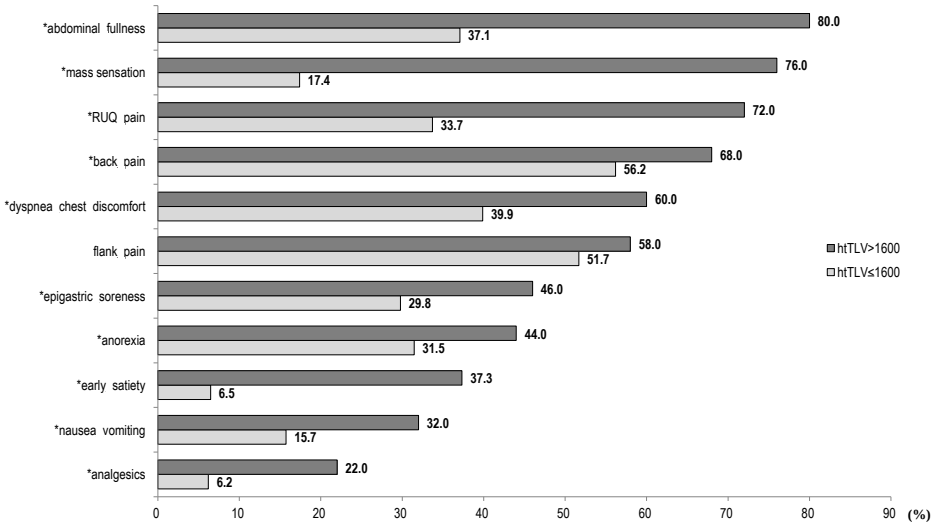
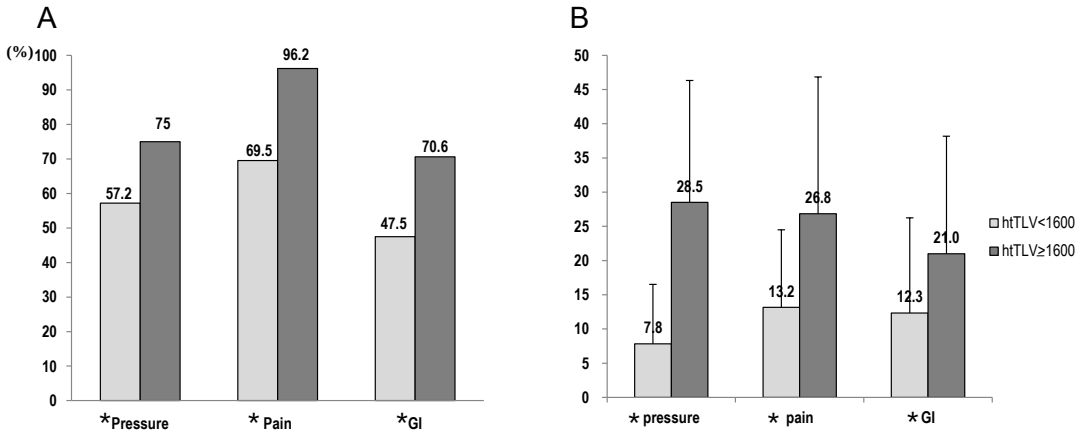


Figure 10. Prevalence and severity of symptoms in the high and low htTLV groups, [a] ANCOVA adjusted for age and sex, * P < 0.001

The 11 items on the questionnaire consisted of GI symptoms (nausea, anorexia, and epigastric soreness), pain (RUQ pain, flank pain, back pain, and analgesics intake), and pressure-related symptoms (early satiety, dyspnea or chest discomfort, palpable mass and abdominal fullness). Since the total scores for the different categories varied, they were standardized on the basis of 100 points to investigate the prevalence [n (%)] and the mean ± SD of each category and of the two groups (Figure 11). Both the prevalence and mean values were significantly higher in the htTLV ≥1,600 group than the htTLV <1,600 group. Whereas the most prevalent symptom in htTLV <1,600 was pain (69.5%), which had the highest mean value (12.2 ± 11.3), pressure-related symptoms (96.2%) was followed by pain (92.3%) and GI (71.2%) in htTLV ≥1,600. For the total score of symptoms in htTLV ≥1,600, pressure had the highest score (37.3 ± 23.4).



htTLV	n	Pressure [n(%]	Pain [n(%]	GI [n(%]
htTLV <1,600	201	115(57.2)	139(69.5)	95(47.3)
htTLV ≥1,600	52	50(96.2)	48(92.3)	37(71.2)
Total	253	165(65.2)	187(73.9)	132(52.2)
[a]*P* value		< 0.001	0.013	0.034

htTLV	n	Pressure (mean±SD)	Pain (mean±SD)	GI (mean±SD)
htTLV >1,600	201	9.0±10.7	12.2±11.3	8.4±11.0
htTLV ≥1,600	52	37.3±23.4	27.7±20.3	20.1±22.2
Total	253	14.8±18.3	15.4±15.0	10.8±14.8
[a]*P* value		< 0.001	< 0.001	< 0.001

[a] ANCOVA adjusted for age and sex, * P < 0.05

Figure 11. Prevalence and severity of symptoms in the high and low htTLV groups. (A) Prevalence of symptoms (B) Severity (mean ± SD) of symptoms

5. Risks of symptoms according to 3 categories

The risks of symptoms were determined by multivariate analysis. The variables significantly related to the prevalence of complications in the univariate analysis ($P < 0.005$) were age, sex, htTLV, CKD stages 3 and 5, Ln(htTKV), albumin, AST, TC, and ALP. Continuous variables were tested to confirm that they satisfied the linear assumption. No significant interaction were observed among the variables. Table 8 shows the odds ratios (ORs) for the prevalence of symtoms. In females, the OR for pressure related symptoms compared to males was 2.18. An htTLV ≥1,600 mL/m was significantly associated with pressure-related symptoms in multivariated model (OR: 4.98, 95% confidence interval [CI]: 1.07–23.26); a similar trend was observed for an htTLV ≥ 2,100 mL/m in pain but htTLV ≥1,600 mL/m was not significant in multivariated model. Meanwhile, ln(htTKV) was not significantly associated with the prevalence of symptoms in the adjusted (model 1 and model 2) models, confirming that htTKV weakly influences hepatic symptoms. Albumin and total cholesterol were associated with pressure related symptoms in the age- and sex-adjusted models but not in the multivariate model. In GI symptoms, neither htTLV ≥ 2,100 mL/m nor htTLV ≥1,600 mL/m did not have association. Rather female sex and CKD stage 3 and 5 were associated with the prevalence of GI symptoms in model2.

Table 8. Multiple binominal logistic regression analysis of symptoms according to 3 categories

variables	group	subject	Pressure			Pain			GI		
			Univariated	Model 1*	Model 2†	Univariated	Model 1*	Model 2†	Univariated	Model 1*	Model 2†
		n	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
sex	male	128					reference				
	female	125	3.03(2.02-4.55)	2.08(1.21-3.56)	2.18(1.22-4.07)	1.95(1.35-2.82)	2.14(1.18-1.02)	2.39(1.24-4.60)	1.60(1.12-2.30)	1.97(1.19-3.27)	2.07(1.16-3.67)
age		253	1.01(1.01-1.02)	1.02(1.02-1.03)		1.02(1.02-1.03)	1.02(1.01-1.02)		1.00(0.99-1.01)		
htTLV	htTLV<2100	219					reference				
	htTLV≥2100	34	33.0(4.51-241.28)	16.81(2.24-126.35)		16.00(3.83-66.76)	4.81(1.10-21.04)	2.39(1.24-4.60)	2.40(1.15-5.02)		
	htTLV<1600	165					reference				
	htTLV≥1600	88	1.34(1.01-1.76)	14.91(3.48-63.80)	4.98(1.07-23.26)	12.00(4.33-33.28)	3.90(1.31-11.58)		2.47(1.35-4.49)	2.34(1.18-4.65)	
CKD stages	stage 1	59					reference				
	stage 2	71	1.37(0.85-2.19)			2.50(1.49-4.20)			0.78(0.49-1.24)		
	stage 3	70	4.00(2.23-7.19)	4.20(1.69-10.43)		3.00(2.40-8.01)			1.69(1.04-2.75)	3.53(1.48-8.39)	2.83(1.20-6.69)
	stage 4	12	2.00(0.60-6.64)			3.00(0.81-11.08)			1.00(3.23-3.01)		
	stage 5	35	4.83(2.01-11.64)	4.57(1.44-14.50)		4.83(2.01-11.64)			2.89(1.35-6.17)	6.18(2.09-18.21)	4.20(1.41-12.56)
LnhtTKV		248	1.11(1.06-1.15)			1.17(1.12-1.22)			1.02(0.98-1.06)		
albumin		241	1.14(1.08-1.22)			1.26(1.18-1.34)			1.02(0.96-1.08)		
AST		241	1.03(1.02-1.04)			1.05(1.04-1.07)			1.00(0.99-1.02)		
TC		241	1.00(1.00-1.00)	1.00(1.00-1.00)		1.01(1.00-1.01)			1.00(1.00-1.01)		

ALP	241	1.01(1.01-1.02)	1.02(1.00-1.03)	1.02(1.01-1.02)	1.00(1.00-1.01)

* model 1: adjusted for age and sex

† model 2: model1 + adjusted for Ln(htTKV), CKD stage, albumin, total cholesterol, AST, ALP, The insignificant items in the adjusted model were left in blank.

PART III

Relationship between htTLV and hepatic complications

1. Prevalence and likelihood of hepatic complications

The families of 54 subjects of the study population were analyzed. Hepatic complications in all patients are shown in Figure 12-A. The most common complication was ascites (16.6%), followed by bilateral leg edema (5%), hernia (3.6%), and cyst infection (3.1%). Meanwhile, the likelihood of having at least one pressure-related complication (log odds) according to htTLV is shown in Figure 12-B; because this graph is a trend line of the complications according to htTLV and the total number of events was small, part of the log odds is expressed as negative numbers. At an htTLV of approximately 2,100 mL/m, the odds of having complications increased with increasing htTLV ± 2SD. Therefore, the cut-off of hepatomegaly was set to an htTLV of 2,100 mL/m; thus, the patients were divided into the htTLV <2,100 and ≥2,100 mL/m groups.

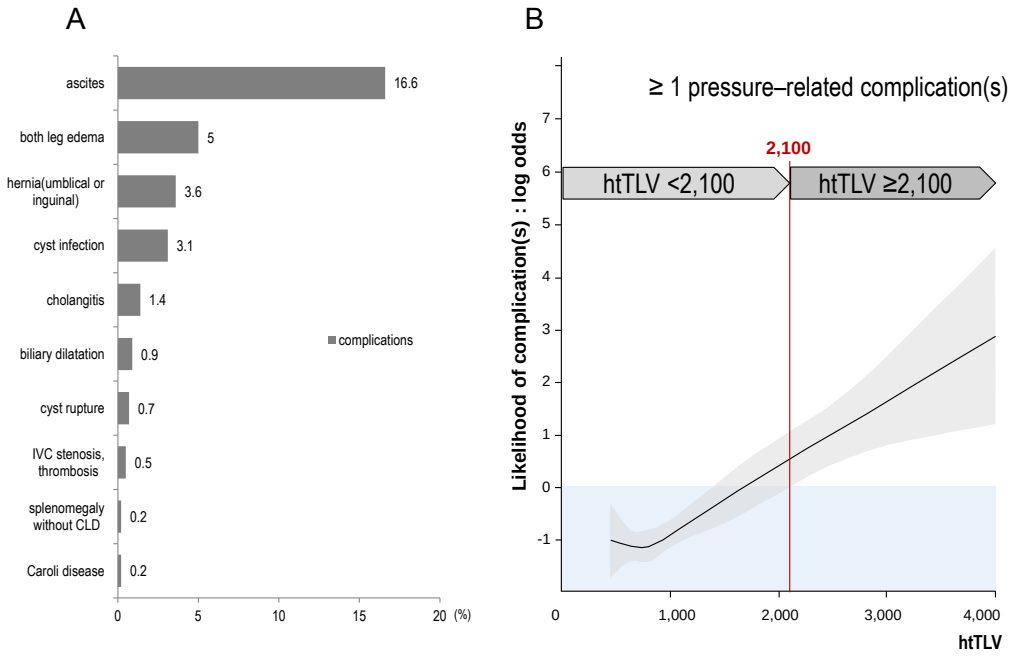


Figure 12: Prevalence and likelihood of hepatic complication(s). (A) Prevalence of hepatic complications in all subjects (B) Likelihood of having more than one pressure-related complication(s). because this graph is a trend line of the complications according to htTLV and the total number of events was small, part of the log odds is expressed as negative numbers.

2. Distribution of htTLV according to a cut-off of 2,100 mL/m

The distribution of htTLV of all subjects and by sex is shown in Figure 13. The htTLV ≥2,100 mL/m group contained a significantly higher percentage of females than males (Figure 13-B and C). The percentages of the htTLV ≥2,100 mL/m group were mostly female regardless of age group (Figure 13-D).

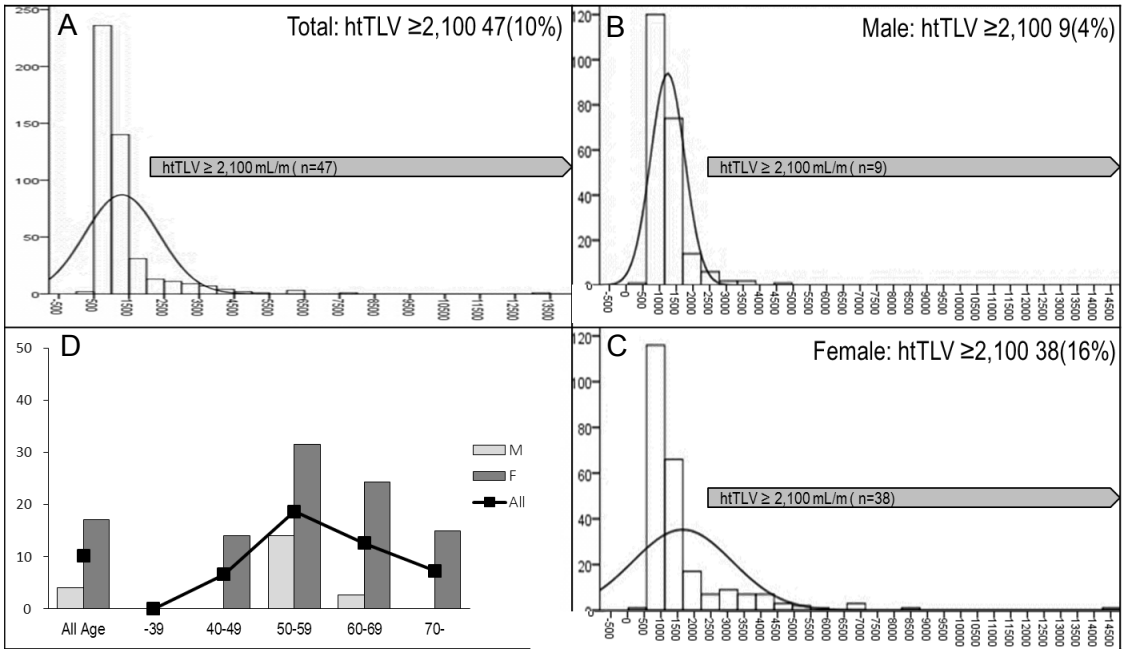


Figure 13: Distribution of the htTLV <2,100 and ≥2,100 mL/m groups by sex and age group, A. Distribution of htTLV in all subjects; B. Distribution of htTLV in males; C. Distribution of htTLV in females; D. Distribution of htTLV according to age groups and sex. Sex differences in all age groups, P < 0.001, χ^2 test

3. Comparison of clinical characteristics

The clinical characteristics of patients according to a cut-off of 2,100 mL/m are shown in Table 9. There were a total of 461 patients. Age and sex-adjusted ANCOVA was used analyze intergroup differences. The percentages of each group were 90% (htTLV < 2,100 mL/m) and 10% (htTLV ≥ 2,100 mL/m). The proportion of females was significantly higher in the htTLV ≥ 1,600 mL/m group than in the htTLV <1,600 mL/m group. The mean age of htTLV <1,600 mL/m group was significantly less than that of the htTLV ≥1,600 mL/m group. The median htTLV in the htTLV <1,600 and ≥1,600 mL/m groups was 957 and 3,173 mL/m, respectively; the means were 762 and 1,351 mL/m, respectively. The incidence of hypertension did not differ significantly between the htTLV <1,600 and ≥1,600 mL/m groups. The mean eGFR was significantly lower in the htTLV ≥1,600 mL/m group. Regarding CKD stage, most patients in the htTLV rding CKD stage, were in Stages 1 and 2. Meanwhile, there were significantly more patients in Stage 5 in the htTLV <2,100 mL/m group than the htTLV <1,600 mL/m group. Liver transplantation, lobectomy, and hepatic embolization were defined as interventions. The htTLV <1,600 mL/m group did not have cases that received interventions, whereas 13 (28%) cases received in the htTLV ≥1,600 mL/m group. Regarding laboratory findings, the htTLV had the lowest levels of albumin and total cholesterol.

Table 9: Clinical characteristics according to htTLV of 2,100 mL/m

All: 461		All	htTLV <2,100	htTLV ≥2,100	P value [a]
n(%)		461(100)	414(90)	47(10)	
Female [n(%)]		241(52)	203(49)	38(81)	<0.001
Age [mean ± SD}		51.3 ± 12.6	50.8 ± 12.9	56.4 ± 7.6	<0.001
htTLV [median(IQR)]		986(825, 1280)	957(813,1147)	3173(2675,4004)	<0.001
htTKV [median(IQR)]		820(453, 1345)	762(424,1301)	1351(891,2204)	<0.001
HTN [n(%)]		365(79.2)	322(78)	43(92)	0.108
eGFR * (CKD-EPI)		80.0 ± 27.7	73.0 ± 27.8	58.8 ± 21.7	<0.001
CKD stage	Stage 1	101(22.7)	99(24)	2(4)	0.003
	Stage 2	132(29.7)	123(30)	9(19)	
	Stage 3	94(21.1)	80(19)	14(30)	
	Stage 4	24(5.4)	23(6)	1(2)	
	Stage 5	94(21.1)	76(18)	18(38)	
Intervention [b]		13(3)	0	13(28)	
Albumin [mean ± SD]		4.3 ± 0.4	4.3 ± 0.3	3.8 ± 0.6	<0.001
TC [mean ± SD]		175.1 ± 30.1	177.3 ± 28.8	153.6 ± 33.6	<0.001

[a] ANCOVA adjusted for age and sex. [b] Intervention: LT, lobectomy and hepatic embolization.* excluded RRT or KT (94 cases), Abbreviations: htTLV, height-adjusted total liver volume; htTKV, height-adjusted total kidney volume, HTN, hypertension, eGFR (CKD-EPI), estimated glomerular filtration rate (Chronic kidney disease epidemiology); TC total cholesterol

4. Prevalence of complications according to a cut-off of htTLV of 2,100 mL/m

The complication frequencies of the htTLV <2,100 and ≥2,100 mL/m groups are shown in Figure 14. Because small and moderate-to-large ascites might have different clinical implications, ascites were categorized as small-to-large or moderate-to-large. Small-to-large ascites was the most frequent complication, which was observed in 55.3% of patients with an htTLV ≥2,100 mL/m. The next most common complication was bilateral leg edema, which was observed in 44.7% of patients with an htTLV ≥2,100 mL/m who had Grade 1 or higher pitting edema. More patients had bilateral leg edema in the htTLV ≥2,100 mL/m group than the other groups. These were followed by hernia (umbilical and inguinal), cyst infection, and moderate-to-large ascites. Besides biliary dilatation, splenomegaly, and Caroli disease, all complications were significantly more common in the htTLV ≥ 2,100 mL/m group than the other groups.

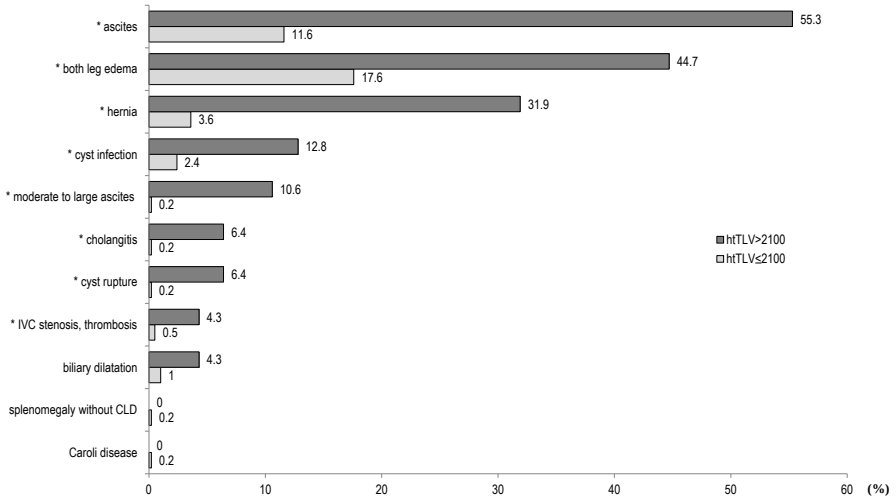


Figure 14: Prevalence of complications in the high and low htTLV groups, ANCOVA adjusted for age and sex, * P < 0.001

5. Risks of complications

The risks of complications were determined by multivariate analysis. The variables significantly related to the prevalence of complications in the univariate analysis ($P < 0.005$) were age, sex, htTLV, CKD stages 3 and 5, ln(htTKV), albumin, AST, TC, and ALP. Continuous variables were tested to confirm that they satisfied the linear assumption. No significant interaction were observed among the variables. Table 10 shows the odds ratios (ORs) for the prevalence of complications in the htTLV <2,100 and ≥2,100 mL/m groups. In females, the OR for complications compared to males was 14.3. An htTLV ≥2,100 mL/m was significantly associated with complications (OR: 14.30, 95% confidence interval [CI]: 3.28–62.19); a similar trend was observed for an htTLV ≥1,600 mL/m, but the ORs were higher for an htTLV ≥ 2,100 mL/m. Meanwhile, ln(htTKV) was not significantly associated with the prevalence of complications in the multivariate model, confirming that htTKV weakly influences hepatic complications. Albumin and total cholesterol were associated with complications in the age- and sex-adjusted models but not in the multivariate model.

Table 10. Multiple binominal logistic regression analysis of complications

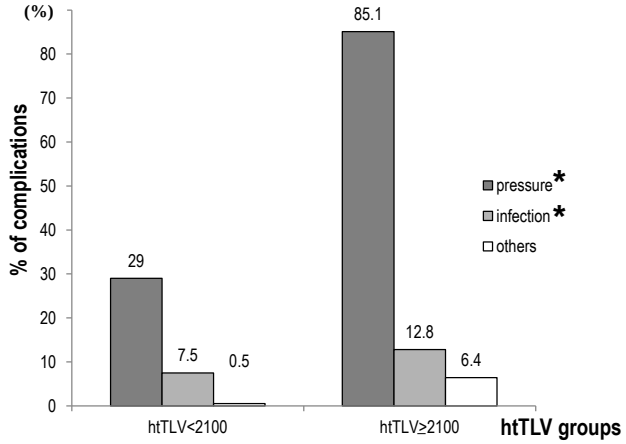
Variables	Group	Subjects n	Univariate OR (95% CI)	Model 1* OR (95% CI)	Model 2† OR (95% CI)
Sex	male	220		1(reference)	
	female	241	3.11(2.07-4.68)	3.04(2.01-4.59)	3.64(1.87-7.07)
age		461	1.03(1.01-1.04)	1.03(1.01-1.04)	1.01(0.98-1.04)
htTLV	htTLV< 2,100	414		reference	
	htTLV≥ 2,100	47	14.00(6.10-32.13)	10.41(4.47-24.25)	14.30(3.28-62.19)
CKD stages	htTLV< 1,600	385		reference	
	htTLV≥ 1,600	76	9.76(5.44-17.52)	7.98(4.36-14.61)	8.44(3.23-22.03)
	stage 1	101		1(reference)	
	stage 2	132	1.46(0.78-2.72)		
	stage 3	94	4.41(2.34-8.32)	4.93(2.32-10.48)	
	stage 4	24	2.03(0.76-5.40)		
	stage 5	94	3.42(1.81-6.45)	3.09(1.40-6.82)	
Ln(htTKV)		451	1.73(1.32-2.25)	1.79(1.34-2.41)	
albumin		424	0.27(0.16-0.47)	0.42(0.23-0.75)	
AST		424	1.02(1.00-1.05)		
TC		425	0.99(0.99-1.00)		
ALP		424	1.01(1.00-1.02)	1.01(1.00-1.02)	
Ln(hsCRP)		269	1.23(1.10-1.39)	1.24(1.09-1.42)	1.22(1.01-1.47)

* model 1: adjusted for age and sex

† model 2: model1 + adjusted for htTLV < or ≥2,100, Ln(htTKV), CKD stage, albumin, total cholesterol, ALP and Ln(hsCRP), The insignificant items in the adjusted model were left in blank.

8. Prevalence of complications by category

The prevalence rates of complications in the htTLV <2,100 and ≥2,100 mL/m groups are shown in Figure 15. Complications were classified as pressure, infection, or other and are presented as events per person. Among the 461 patients, 181 complications were observed, including 132 and 49 in the htTLV <1,600 and ≥1,600 mL/m groups, respectively. The frequencies of all categories of complications were significantly higher in the htTLV ≥1,600 mL/m group than the htTLV <1,600 mL/m group. Accordingly, the prevalence of complications was significantly higher in the htTLV ≥2,100 mL/m group than the htTLV <2,100 mL/m group. Table 11 shows the ORs of the prevalence of complications according by group. The htTLV ≥2,100 mL/m group was significantly associated with pressure-related complications (OR: 12.65, 95% CI: 3.11–51.54). Regarding infections, the htTLV ≥2,100 mL/m group showed a significant OR in the age- and sex-adjusted model (OR: 6.27, 95% CI: 1.99–19.76) but not in the multivariate model.



*: p-value <0.001

Figure 15. Prevalence of complications by category in the high and low htTLV groups

Table 11. Multiple binominal logistic regression analysis of complications: subanalysis

n = 458		Model 1*		Model 2†
	n	OR (95% CI)	n	OR (95% CI)
		Pressure-related		
htTLV <2,100	414	1 (reference)	231	1 (reference)
htTLV ≥2,100	47	10.38(4.45-24.168)	31	12.65(3.11-51.54)
P value		< 0.001		< 0.001
		Infection (cholangitis or cyst infection)		
htTLV<2,100	414	1 (reference)	231	1 (reference)
htTLV≥2,100	47	6.27(1.991-19.76)	31	2.92(0.43-19.9)
P value		0.002		0.273

ANCOVA adjusted for age and sex, * P-value <0.001

* model 1: adjusted for age and sex

† model 2: model1 + adjusted for Ln(htTKV), CKD stage, albumin, total cholesterol, AST, ALP and Ln(hsCRP)

PART IV

Familial distribution of massive liver disease in ADPKD

15. Familial distribution of htTLV by sex

The distribution of htTLV among 54 families and 123 patients aged 22–78 years (mean: 51.5 ± 13.2 years) was analyzed. The male/female ratio was 1:0.95. Most members of the 54 families had an htTLV <2,100 mL/m. Below the age of 40, subjects with htTLV ≥1,600 mL/m was not observed. Besides family #37, no family had 2 or more members with an htTLV ≥2,100 mL/m. 11 (20.4%) families had 1 member with an htTLV ≥2,100 mL/m. Moreover, 5 families had ≥2 members with an htTLV ≥1,600 mL/m. Furthermore, 20 families (37%) had 1 member with an htTLV ≥1,600 mL/m. Among the 11 families with severe liver disease, 9 included female patients. In the case of family #15, one of the two brothers in their 50s had a normal liver volume, while the other had an htTLV ≥2,100 mL/m. In the case of family #23, one of the two brothers in their 60s had an htTLV of 2,084 mL/m, while the other had an approximately normal htTLV of 1,346 mL/m. In family #36, a man in his forties had a higher htTLV than a woman in her thirties.

The htTLV distributions of siblings in 20 families among 45 families are shown in Figure. The baseline characteristics are presented by 10-year age groups (e.g., only siblings in their 50s). Family #37 included a brother and a sister who had an htTLV ≥2,100 mL/m. In the case of family #18, one sister had an htTLV <2,100, but both sisters had an htTLV ≥1,600 mL/m. Among the 20 families, the sisters in families #14 and #50 exhibited large differences in their htTLVs. In 4 families (#14, #15, #18, #23), large differences in htTLV were observed between brothers and sisters. Meanwhile, 12 families did not exhibit significant differences in htTLV between brothers and sisters, whereas the remaining 8 did. This indicates a large variation in siblings' htTLV.

There were few common morbidity cases between siblings. The brothers in 2 families (#15, #23) with massive liver disease exhibited a discrepancy.

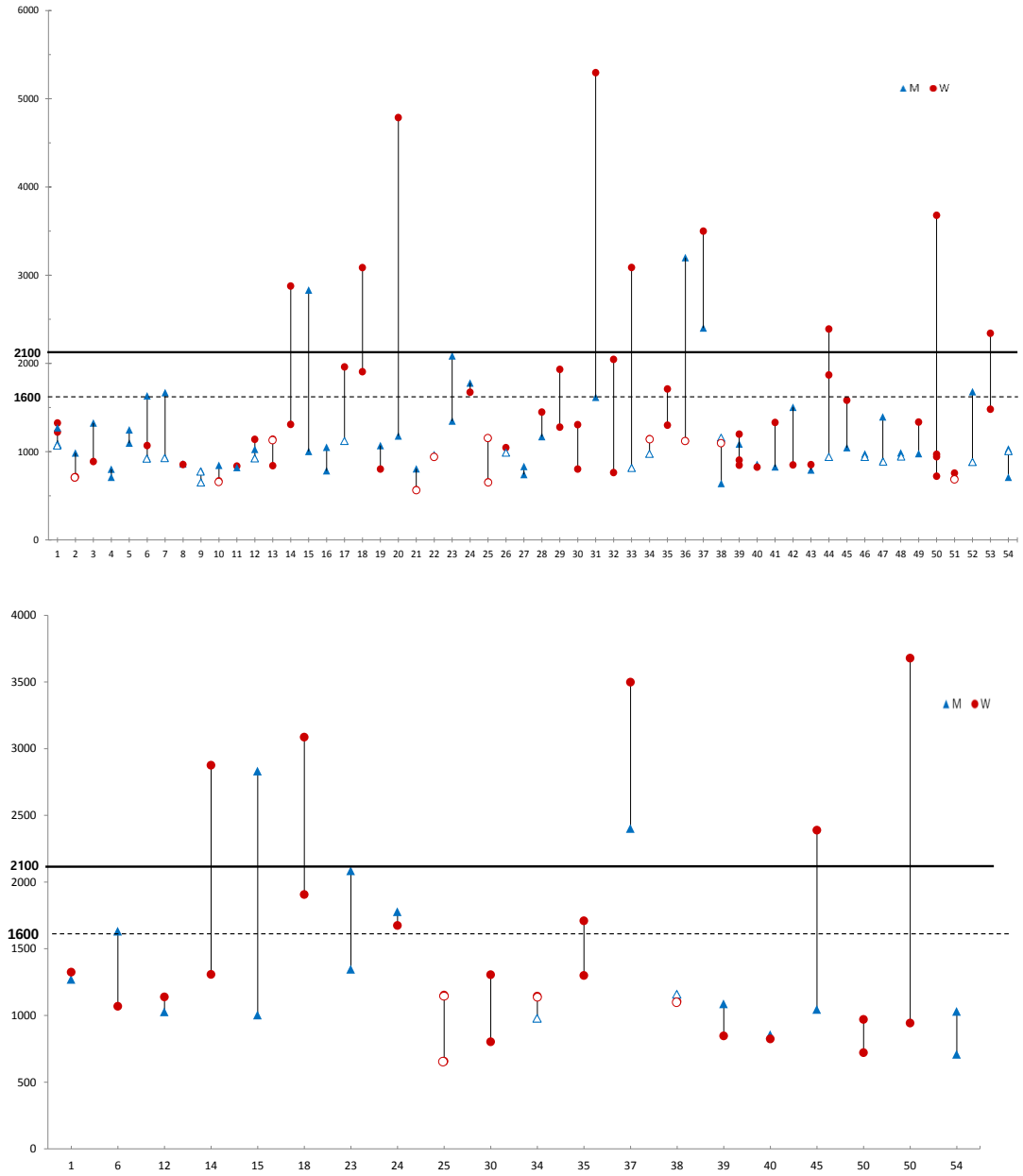


Figure 16. Familial distribution of htTLV by sex. Numbers on the x-axis represent unique family numbers. On the y-axis, 1,600 and 2,100 indicate the cut-offs for symptoms and complications, respectively. Empty circles (females) and triangles (males) indicate subjects aged <40 years; solid circles and triangles indicates subjects aged ≥40 years. (A) Familial distribution of htTLV by sex in 54 families. Only 1 family (#37) had 2 members with htTLV ≥2,100 mL/m, and 11 (20.4%) families had 1 member with htTLV ≥2,100 mL/m. Five families had 2 members with htTLV ≥1,600 mL/m and 20 (37%) families had 1 member with htTLV ≥1,600 mL/m. (B) Distributions of htTLV among siblings in 20 families. Only 1 family's siblings (#37) had 2 members with htTLV ≥ 2,100 mL/m, and 6

(30%) siblings had 1 member with htTLV ≥2,100 mL/m. Three siblings had 2 members with htTLV ≥1,600 mL/m and 10 (50%) siblings had 1 member with htTLV ≥1,600 mL/m.

Figure 17 shows familial distribution where the family member with the largest liver was set as proband and then plotted along the x-axis, and the remaining family members (over 40 years old) were plotted along the htTLV when severe liver disease was defined as htTLV $\geq$1,600 mL/m. The mean htTLV was presented as the mean htTLV of the remaining family members, except for the proband of each family. Graph A and Table 12 presents the plotting of 54 families, showing that the mean htTLV was higher in the families with htTLV $\geq$1,600 than in those with htTLV <1,600. No significant difference in the age and gender ratio was found between the two groups. In addition, Graph B and Table 12 presents the sibling distribution of htTLV, showing no significant difference in the htTLV between the two groups.

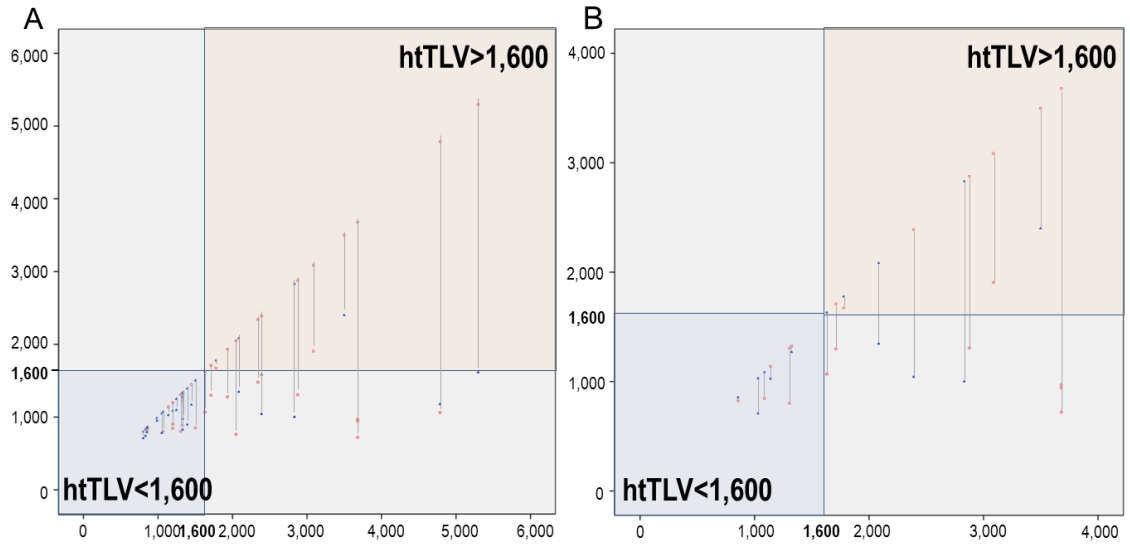


Figure 17. Differences between the 2 groups according to the htTLV of probands (above 40 years old). (A) Familial distribution of htTLV with the probands set along the x-axis. (B) Sibling distribution of htTLV with the probands set along the x-axis

Table 12. Mean htTLV according to htTLV <1,600 and ≥1,600 mL/m excluding probands

	<1,600	≥1,600	P value	htTLV	<1,600	≥1,600	P value
n	16	24		n	6	12	
htTLV (Mean ± SD)	915 ± 156	1,375 ± 400	<0.001	htTLV (Mean ± SD)	912 ± 203	1,306 ± 476	0.082
Age	53.4 ± 1.8	57.8 ± 7.9	0.166	Age	53.4 ± 1.8	57.8 ± 7.9	0.888
Female, n(%)	6(38)	13(54.2)	0.349	Female, n(%)	3(50)	4(33)	0.506

[a] ANCOVA adjusted for age and sex

DISCUSSION

In summary, in Part I, the prevalence of hepatic cyst involvement in ADPKD was 91.8% in 461 ADPKD patients. The mean htTLV was significantly different between female and male patients (1,492 vs. 1,086 mL/m). The median htTLV of female patients increased with age ($P < 0.001$). Hepatomegaly (3T, 4Q) was more common among female patients. Furthermore, htTLV was well correlated with htTLV+htTKV (i.e., intra-abdominal mass, $R^2 = 0.625$, $P < 0.001$). In Part II, back pain, flank pain, and abdominal fullness were common symptoms in all patients. At an htTLV cut-off of 1,600 mL/m, the possibility of having at least 2 pressure-related symptoms increased with increasing htTLV. At htTLV ≥1,600 mL/m, kidney function was reduced and albumin and cholesterol levels were lower; however, the prevalence of hypertension was not elevated. Furthermore, an htTLV ≥1,600 mL/m was associated with an increased prevalence and severity of pain and GI symptoms. In Part III, ascites, bilateral leg edema, hernia, and cyst infection were common complications. At an htTLV cut - off of 2,100 mL/m, the risk of pressure-related complications increasing with increasing htTLV. Patients with an htTLV ≥2,100 mL/m were older, included more females, had higher Ln(htTKV), had a higher prevalence of CKD stage 5, and had lower levels of albumin and total cholesterol. In multivariate models, an htTLV ≥2,100 mL/m was significantly associated with pressure-related complications but not infection. Furthermore, complications increased significantly at both htTLV cut-offs; however, the ORs were higher with a cut-off of 2,100 mL/m. In Part IV, in the families with htTLV ≥1,600 mL/m with a proband, the mean htTLV level of the members excluding the proband was significantly higher than that of families with htTLV <1,600 without a proband (P = 0.001). However, few common morbidity cases were observed between siblings.

The hottest issue in hepatic cysts in ADPKD is TLV measurement. Since 1979, the ideas of reconstructing 3-D CT images of organs were suggested (15, 16), and they are still widely used. However, the automatic process of 3-D reconstruction in ADPKD patients has not been developed yet. The reason of the difficulty in measuring the automated TLV in ADPKD is the difficulty in figuring out the liver outline. Since CT and MRI recognize the organs using the difference in Hounsfield unit (HU) or signal intensity (SI), practically the normal kidney and

liver are clearly differentiated from other structures, and when the region-based threshold method is used, the organ volume can be easily measured (15, 17, 18). In the case of ADPKD patients, however, the exact boundary of their liver is hardly recognizable due to the irregular cyst growths. Moreover, the boundary between the liver cyst and kidney cyst is unclear in the case of large TLV patients due to the considerably large area overlapping with the polycystic kidney. In this study, the typical semi-quantitative and semi-automatic 3-D reconstruction method was used to measure the TLV, but this is a labor-intensive manual method requiring one hour per case, making it difficult to be used in clinical cases (19). Therefore, it is necessary to develop a marker indicating the liver, so liver linearization may be realized for TLV measurement in ADPKD.

Regarding the prevalence of liver cyst involvement, in the current data, 96.8% of the female subjects and 74% of the male subjects younger than 39 years had liver cysts. These findings mean liver cysts may develop earlier in women than men. In the 40-or-older males and females, more than 90% of them showed liver cysts involvements. This can be interpreted to mean that the hepatic cyst involvement can be confirmed in more than 90% of individuals aged ≥40 years.

To determine the onset time of the liver cyst, we need more samples and information on the pregnancy history and the experience of hormone therapy. According to previous studies, the prevalence of liver cyst involvement of in males and females was the same, but in this study, the female hepatic cyst prevalence was higher than that of males in all age groups with statistical significance. In particular, in the group younger than 39 years of age, the prevalence was significantly higher in females than males. A previous study reported that the prevalence of hepatic cysts in 25 to 34 years by sex was 91% in females and 75% in males. Therefore, my results correspond to those of the previous study (5).

No statistically significant difference in htTLV was observed between males and females, but in terms of htTLV distribution and hepatomegaly proportion, significantly more cases were found in females than in males. The reason for the greater hepatomegaly frequency in females than in males is due to the effects of sex hormones. Estrogens have been shown to enhance the proliferative and secretory activities of cholangiocytes when they bind to estrogen receptors and

activate several growth factors (7), but no additional specific reasons have been reported so far. However, in the male subjects aged over 60, the htTLV appeared to slightly decrease with age; but in the female subjects, the htTLV consistently increased with age. In the case of women, it was found that the htTLV median increased as age increased, while, in the case of men, it decreased after their 60s. This means that the older men with a large liver size are difficult to find, and cause of this phenomenon needs to be researched. Since this study was based on cross-sectional data, we cannot assume an age-related liver growth rate. To understand the pattern of the liver size with age, we had to measure the serial liver size of each patient. Second, since the mortality rate of male subjects aged ≥60 years with a large liver may be higher than that of the female subjects, this phenomenon may also denote a kind of selection bias. Third, the consideration of sex difference or hormonal influence or genetic distribution is needed.

In this study, htTLV distribution and its complications were investigated. It has been known that TKV is important for predicting kidney outcomes; the GFR reduction rate decreases significantly according to the levels of TKV > 750 mL/m and 1500 mL/m; and the baseline htTKV is the most influential factor in predicting renal progression. (20, 21). Therefore, this study is based on the assumption that TLV can help predict the prevalence and severity of the hepatic symptoms and complications.

The prevalence of the symptoms according to the htTLV was also investigated. Because symptoms develop from physical organ enlargement, the kidney size could influence the symptom prevalence. Therefore, it may be practically difficult to separate the liver symptoms from the kidney symptoms, and this was the limitation of the questionnaire. Suwabe et al. (22) analyzed quality of life in the integrated htTKV and htTLV cases using SF-36. In some symptoms, this integration helped explain quality of life. However, the focus of this study was the prevalence of the symptoms according to the change in the htTLV, so only the htTLV was analyzed. Additionally in adjusted model, htTKV was not associated with the prevalence of symptoms. Therefore I didn’t take into consideration of htTKV in symptom analysis. In symptom investigation, I modified a previously validated questionnaire to investigate the relationship between htTLV and symptom severity. Overall, both groups showed high frequencies of pressure-related symptoms, pain, and GI tract symptoms. The frequency and

mean score of the htTLV ≥1,600 mL/m group was higher than those of the htTLV <1,600 mL/m group. This meant that the ADPKD patients complained of various symptoms that deteriorated their quality of life. As expected, the htTLV ≥1,600 mL/m group had a worse quality of life than the htTLV <1,600 mL/m group. Meanwhile, many patients complained of pain. Compared to the high prevalence of pain, the relative prevalence of analgesics intake was low. However, the information gathered from patient interviews suggests many patients might have decided not to take analgesics for their kidney function, even though they needed them.

In the case of symptoms, symptoms were classified from grade 0–3 as per the existing literature by referring to the Gastrointestinal Symptom Rating Scale (GSRS). Notably, abdominal fullness was a specific symptom which could be seen only in hepatic manifestations. Scoring, which expresses difficulty in ordinary life, may be subjective. Notably, it may be different according to sex and age, but a more systematic questionnaire needs to be written by correcting such problems or by coming up with a new questionnaire. Only outpatients were surveyed; of 461 patients, only 253 patients were surveyed. As patients who underwent liver transplantation, hepatectomy, or hepatic embolization were excluded from the survey, the symptom prevalence in the htTLV ≥1,600 mL/m group might increase significantly if the patients who had an intervention were included. Thus, the result may be somewhat different from the actual ADPKD patient distribution. Also, the subjects of this survey also included 35 CKD stage 5 patients. GI symptoms, which may occur as uremic symptom manifestation due to ESRD, may not be distinguished from hepatic symptom. Thus, CKD stage 5 patients may need to be excluded in additional analysis. Also, to assess symptom severity, severity was graded from 0–3, but the frequency of scoring 2 or more was low; furthermore, the analysis was conducted based on the presence or absence of symptom. This problem can be addressed when increasing the sample size, and future research needs to increase the number of subjects. In the graph of htTLV and possibility of symptom, as expected, the OR of the pressure-related symptoms was significantly high at 1,600 or higher htTLV levels. Interestingly, however, pain was not significant in the multivariated model at htTLV 1600, but significant at htTLV 2,100. Since pain was prevalent in large-liver patients, and htTLV 2100 was highly associated with the complications such as infection and ascites, pain could be caused by the mechanisms other than the pressure

mechanism. The GI symptoms were not associated with htTLV in the multivariated model. They were significant in females and CKD stages 3 and 5 because the CKD stage was relatively a strong impact factor in the GI symptoms. Further evaluations on the relations between the GI symptoms and htTLV may be necessary in the future.

The prevalence rates of complications according to the htTLV were also investigated. In all subjects, bilateral leg edema was the most common complication. It was assumed in this study that even though bilateral leg edema does not result in total compression against the large blood vessels, edema can develop due to possibility of portal or IVC compression. Based on this assumption, the prevalence of bilateral leg edema was investigated. It was found to have been more prevalent in the htTLV ≥2,100 mL/m patients, but no clear causal relationship or pathophysiology was found. However, in previous studies, IVC stent insertion resolved leg edema in ADPKD patients (23); therefore, large liver might interfere with venous return in ADPKD patients. In addition, because 17 (34.7%) were CKD stage 5 patients in the htTLV ≥2,100 mL/m group, the possibility that many low-eGFR patients that cannot regulate water balance would be included in the htTLV ≥2,100 mL/m group should be considered.

It is reported that ascites caused by two processes that may lead to portal hypertension: reduction of hepatic vein outflow and compression of portal vein inflow (24). In addition, compression of the IVC can cause increase in renal outflow pressure that provokes development of ascites (25). Despite the prevalence of moderate to large ascites were not high (10.6% in Group 4), some subjects suffered from intractable ascites. Therefore, the management of massive ascites in polycystic liver of ADPKD is another important issue. Hernia was the third most common complication in the htTLV ≥2,100 mL/m group. It is known that the prevalence of umbilical and inguinal hernias may be seen in up to 15–45% of ADPKD patients (26-28) in agreement with the data. Taken together, pressure-related complications such as ascites, bilateral leg edema, and hernia were significantly connected to htTLV.

As for infection, the fourth-most prevalent complications in the data, the OR of htTLV in the multivariate model was insignificant. Actually, some cholangitis or cyst infection cases occurred when the htTLV was 1,000 mL/m. Moreover, 7/16 cases in infection had htTLV <1,600 mL/m. I showed the risk of infection with small liver. First, regarding infection, the location of hepatic

cysts may be more important than size. Most hepatic cysts consist of biliary tract and separation, but are close to biliary tract; thus, peribiliary cyst, which can compress the tract, may more trigger cyst infection or cholangitis than intrahepatic cysts (24). Also, important infection factors, such as the host's immune system, underlying comorbidities, and hepatic cyst intervention may have imposed secondary impact. Lastly, there were only 16 cases with hepatic infection of the total, and the problems related to such a lack of sample size cannot be ruled out. At any rate, it is important to note that infection could occur in relatively small hepatic cysts.

The number and size of hepatic cysts are associated with the occurrence of pregnancy, female sex, age, and severity of the renal lesion (29). In a previous study, when sex hormone therapy was administered to females, their liver size increased significantly compared to the controls (30). Several previous studies report that factors such as estrogen, prolactin progesterone, hormones (including follicle-stimulating hormone), growth factor, and cytokines induce cholangiocyte growth (31). In the present and previous studies, severe massive liver diseases that can induce symptoms and complications were more common in women than in men. Nevertheless, hepatic cysts develop because of various genetic and environmental factors. As observed in family #37, massive hepatic cysts were observed in both sexes mainly due to genetic factors. Meanwhile, in families #14 and #32, the clinical difference of hepatic cysts in the sisters might be affected not only by their obstetric history, but also by unknown environmental factors; however, it is uncertain whether their obstetric histories differed significantly (htTLV and the number of pregnancies of the proband vs. her sister, family #14: 2,876 mL/m and 4 vs. 1,307 mL/m and 3; family #32: 2,046 mL/m and 5 vs. 763 mL/m and 3). As the various clinical characteristics of ADPKD cannot be explained by single genes such as *PKD1* and *PKD2*, massive hepatic cysts may have numerous factors that contribute to their clinical characteristics. However, these risk factors have very little empirical evidence because of the lack of the familial information on massive liver diseases. The accumulation of massive liver disease cases in the future may help elucidate these risk factors, consequently helping diagnose and treat these diseases. Importantly, investigating mutations related to the hepatic involvement of ADPKD, such as genes causing polycystic liver disease (*PRKCSH* and *SEC63*) (24), is crucial for understanding massive liver disease in ADPKD.

This study has several limitations. First, the cross-sectional design makes it impossible to infer causality between the prevalence of symptoms and complications, and htTLV. All the complications that developed since one year before the CT scan, or since October 2008, were investigated. According to previous studies which were mostly small-scale studies, the annual liver cyst growth rate was 0.92%-3.2% (32-34). Considering the negligible changes in the liver size for one year, the one-year window period after the CT scan date may not be a problem in the cross-sectional data analysis. Changes in symptoms and complications with liver cyst growth could not be analyzed. Therefore, a long-term large-scale prospective study is required to corroborate the results. Second, only symptoms and complications related to htTLV were included. Thus, there could be additional symptoms and complications that were not included in this study. Furthermore, the effect of htTKV on hepatic symptoms was not included, although htTKV is reported to also affect symptoms such as back pain and GI symptoms. As a symptom analysis of this study, the possibility of the diseases such as GERD and peptic ulcer, which could cause GI symptoms, was not corrected. Finally, this was a single-center study. Therefore, a selection bias is unavoidable. However, considering that many patients in Korea have been registered in the ADPKD clinic of Seoul National University Hospital, a similar prospective study in this center may produce meaningful results.

In conclusion, the prevalence of the ADPKD symptoms and complications were confirmed to increase as htTLV progresses. This study presented several clinical implications: when the htTLV became larger than 1,600 mL/m, hepatic symptoms would be increase, and in the same manner above 2,100 mL/m, the serious complications that require intervention become significantly prevalent. In addition, there might be familial trends of large liver in ADPKD. These findings are important because they help set important guidelines for the treatment of hepatic cysts.

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국문초록

서론: 상염색체우성다낭신환자에서 간낭종은 자주 가장 흔한 신장 외 증상이다. 본 연구에서는 한국인 우성다낭신 환자 488 명에서 키로 보정한 간부피와 간 관련 증상 및 합병증간의 관계를 조사하였다.

방법: 간낭종의 이환은 컴퓨터 단층촬영에서 적어도 4 개 이상의 간낭종이 있는 경우로 정의하였다. 간 관련 증상 및 합병증을 규명하기 위하여 의무기록을 검토하였으며, 신체검진을 시행하였다. 간 관련 증상을 평가하기 위하여 설문지를 사용하였다. 간부피는 정위적 방법으로 측정하였으며 키로 보정하였다.

결과: 다낭성 간질환의 빈도는 여성에서 보다 흔하였다 (96.2% vs. 86.9%, P <0.001). 모든 대상자에서 흔한 증상에는 허리통증 (59.4%), 옆구리 통증 (53.1%), 복부 팽만감 (46.5%), 호흡곤란 혹은 가슴 불편감 (44.3%)이 있었다. 조기 포만감, 호흡곤란 혹은 가슴 불편감, 덩어리가 만져지는 느낌 및 복부 팽만감을 포함하는 압력 관련 증상 및 통증, 위장관계 증상은 모두 htTLV >1,600 mL/m 과 연관성이 있었다 (P < 0.05). 또한 압력 관련 합병증, 간낭종 감염 및 담도염 역시 htTLV >1,600 mL/m 과 연관성이 있었다 (P <0.001). 흔한 합병증으로는 복수 (16.6%), 양측 다리 부종 (5%), 탈장 (3.6%) 및 낭종 감염 (3.1%)이 있었다. 복수, 탈장, 양측 다리 부종, 담관 확장, 하대정맥 협착을 포함하는 압력 관련 합병증은 다변량 분석에서 htTLV >2,100 mL/m 과 연관성이 있었다. 간낭종 감염 및 담도염 역시 htTLV >2,100 mL/m 은 다변량 분석에서는 연관성이 없었다.

결론: 간 관련 증상은 간부피 htTLV >1,600 mL/m 부터, 간 관련 합병증은 htTLV >2,100mL/m 이상에서 그 빈도가 유의하게 증가하기 때문에 임상가들은 이러한 대상자에 대한 특별한 관심을 가질 필요가 있다.

주요어:상염색체우성다낭신, 간비대, 증상, 합병증, 간부피

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